

# PRV

PATENT- OCH REGISTRERINGSVERKET  
Patentavdelningen

PCT/GB 2004 / 0 0 4 1 3 2

2 4 SEPTEMBER 2004

REC'D 13 OCT 2004

WIPO

PCT

## Intyg Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande AstraZeneca AB, Södertälje SE  
Applicant (s)

(21) Patentansökningsnummer 0302572-3  
Patent application number

(86) Ingivningsdatum 2003-09-26  
Date of filing

Stockholm, 2004-08-02

För Patent- och registreringsverket  
For the Patent- and Registration Office

  
Hjordis Segerlund

Avgift  
Fee 170:-

**PRIORITY DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH  
RULE 17.1(a) OR (b)

PATENT- OCH  
REGISTRERINGSVERKET  
SWEDEN

Postadress/Adress  
Box 5055  
S-102 42 STOCKHOLM

Telefon/Phone  
+46 8 782 25 00  
Vx 08-782 25 00

Telex  
17978  
PATOREG S

Telefax  
+46 8 666 02 86  
08-666 02 86

**BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF**

**5 BACKGROUND OF THE INVENTION**

**1. Field of the invention**

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

**2. Discussion of Relevant Technology**

15 Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB<sub>1</sub> receptor, CB<sub>2</sub> receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB<sub>1</sub> and/or CB<sub>2</sub> receptors. Generally, CB<sub>1</sub> receptors are located predominately in the central nervous system, whereas CB<sub>2</sub> receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

25 While CB<sub>1</sub> receptor agonists, such as  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB<sub>1</sub> receptors located in CNS. There are lines of evidence, however, suggesting that CB<sub>1</sub> agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

30 Therefore, there is a need for new CB<sub>1</sub> receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

**DESCRIPTION OF THE INVENTION**

The present invention provides CB<sub>1</sub> receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

### Definitions

5 Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

10 "CB<sub>1</sub>/CB<sub>2</sub> receptors" means CB<sub>1</sub> and/or CB<sub>2</sub> receptors.

The term "C<sub>m-n</sub>" or "C<sub>m-n</sub> group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

15 The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

25 The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

30 The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

containing structure or molecule has an aromatic character (*e.g.*,  $4n + 2$  delocalized electrons).

5 The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a radical derived from a heterocycle by removing one hydrogen from a carbon of a ring of the heterocycle.

10 The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on a carbon of an aromatic ring of the heterocyclyl.

15 The term "heterocycloalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

20 The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

25 A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

30 A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

5 The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*,  $4n + 2$  delocalized electrons) and comprising 5 up to about 14 carbon atoms,  
10 wherein the radical is located on a carbon of the aromatic ring.

The term "non-aromatic group" or "non-aromatic" used alone, as suffix or as prefix, refers to a chemical group or radical that does not contain a ring having aromatic character (*e.g.*,  $4n + 2$  delocalized electrons).

The term "arylene" used alone or as suffix or prefix, refers to a divalent  
15 hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*,  $4n + 2$  delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms,  
20 independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share  
25 two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

30 The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more

- 5 C<sub>1-12</sub>hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, -NO<sub>2</sub>, -OR, -Cl, -Br, -I, -F, -CF<sub>3</sub>, -C(=O)R, -C(=O)OH, -NH<sub>2</sub>, -SH, -NHR, -NR<sub>2</sub>, -SR, -SO<sub>3</sub>H, -SO<sub>2</sub>R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR<sub>2</sub>, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S),  
10 and oximino (=N-OR), wherein each "R" is a C<sub>1-12</sub>hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

- The term "substituted" used as a suffix of a first structure, molecule or group,  
15 followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

- The term "optionally substituted" refers to both groups, structures, or  
20 molecules that are substituted and those that are not substituted.

- Heterocycle includes, for example, monocyclic heterocycles such as:  
aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine,  
25 piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

- In addition, heterocycle includes aromatic heterocycles, for example, pyridine,  
30 pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-2,4-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl,

xanthenyl, phenoxathiinyl, thianthrenyl, indoliziny, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, 5 pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms 10 common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula  $-O-R$ , wherein  $-R$  is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, 15 cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula  $-O-Ar$ , wherein  $-Ar$  is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula  $-O-Ar'$ , wherein  $-Ar'$  is a heteroaryl.

20 The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula  $-NRR'$ , wherein  $R$  and  $R'$  are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means  $-C(=O)-R$ , wherein  $-R$  is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, 25 for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

30 "RT" or "rt" means room temperature.

A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.



"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

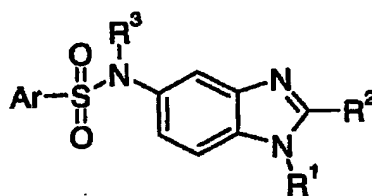
When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

"Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom generally adopts an  $sp^3$  atomic orbital hybridization.

"Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a  $sp$  or  $sp^2$  atomic orbital hybridization.

#### 15 Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

$R^1$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl used in defining  $R^1$  is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

$R^2$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,

C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkyl-C<sub>1-4</sub>alkyl, and C<sub>4-8</sub>cycloalkenyl-C<sub>1-4</sub>alkyl used in defining R<sup>2</sup> is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

R<sup>3</sup> is selected from -H, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, and

5 C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl; and

Ar is selected from C<sub>6-10</sub>aryl and C<sub>3-6</sub>heteroaryl, wherein said C<sub>6-10</sub>aryl and C<sub>3-6</sub>heteroaryl are optionally substituted with one or more groups selected from C<sub>1-3</sub>alkyl, methoxy and halogen.

10 In another embodiment, the compounds of the present invention are those of formula I, wherein

R<sup>1</sup> is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, C<sub>4-6</sub>cycloalkenyl-C<sub>1-4</sub>alkyl and C<sub>3-6</sub>heterocycloalkyl-C<sub>1-4</sub>alkyl, wherein said C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, C<sub>4-6</sub>cycloalkenyl-C<sub>1-4</sub>alkyl and C<sub>3-6</sub>heterocycloalkyl-C<sub>1-4</sub>alkyl used in defining R<sup>1</sup> is optionally substituted by one or  
15 more groups selected from halogen, methoxy, ethoxy, methyl, hydroxy and amino;

R<sup>2</sup> is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, and C<sub>4-6</sub>cycloalkenyl-C<sub>1-4</sub>alkyl, wherein said C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, and C<sub>4-6</sub>cycloalkenyl-C<sub>1-4</sub>alkyl used in defining R<sup>2</sup> is optionally substituted by one or more groups selected from halogen,  
20 methoxy, ethoxy and hydroxy;

R<sup>3</sup> is selected from -H and C<sub>1-3</sub>alkyl; and

Ar is selected from phenyl and C<sub>3-6</sub>heteroaryl, wherein said phenyl and C<sub>3-6</sub>heteroaryl are optionally substituted with one or more groups selected from methyl, methoxy, fluoro, chloro, bromo and iodo.

25

In a further embodiment, the compounds of the present invention are those of formula I,

wherein R<sup>1</sup> is selected from cyclopentyl-methyl, cyclohexyl-methyl, cyclobutyl-methyl, tetrahydropyranyl-methyl, tetrahydrofuranyl-methyl, morpholinyl-methyl, piperdinylethyl, N-methyl-piperdinyl-methyl and piperdinyl-methyl;  
30

R<sup>2</sup> is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-methoxy-2-propyl, 2-hydroxy-propyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-buten-1-yl, ethyl, and 2-propyl;

$R^3$  is selected from -H and methyl; and

Ar is selected from phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl, wherein said phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl are optionally substituted with one or more  
5 groups selected from methyl, methoxy, fluoro and chloro.

In an even further embodiment, the compounds of the present invention are those of formula I, wherein

10  $R^1$  is cyclohexyl-methyl;

$R^2$  is t-butyl;

$R^3$  is selected from -H and methyl; and

Ar is selected from phenyl, pyridyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl, wherein said phenyl, pyridyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl are optionally substituted with one or more methyl groups.

15

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or  
20 mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may  
25 exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I.

It will also be understood that certain compounds of the present invention may  
30 exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I.

Within the scope of the invention are also salts of the compounds of the formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a  
5 suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a  
10 carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt  
15 such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB1 receptors. More particularly, the  
20 compounds of the invention exhibit selective activity as agonist of the CB1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other  
25 disease states in which dysfunction of CB1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for  
30 autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to  
5 administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for  
10 the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically,  
15 intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the  
20 disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid.  
25 Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

30 In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

5        Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

10        The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

15        Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

20        Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

25        Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

30        A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I for the manufacture of a medicament for the therapy of pain.

5        Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

10        A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such therapy.

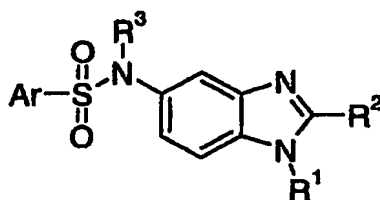
15        Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

20        Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

25        In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of formula I,

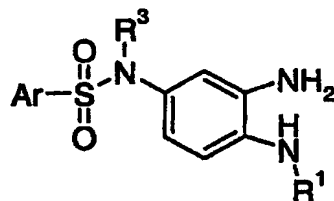


I

30        comprising:



reacting a compound of formula II,



**II**

with a compound of  $R^2\text{COX}$ , in the presence of a base, such as an alkylamine, and  
 5 optionally a coupling reagent, such as HATU, EDC;  
 wherein

X is selected from Cl, Br, F and OH;

$R^1$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  
 $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  
 10  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl used in defining  $R^1$  is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

15  $R^2$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl used in defining  $R^2$  is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

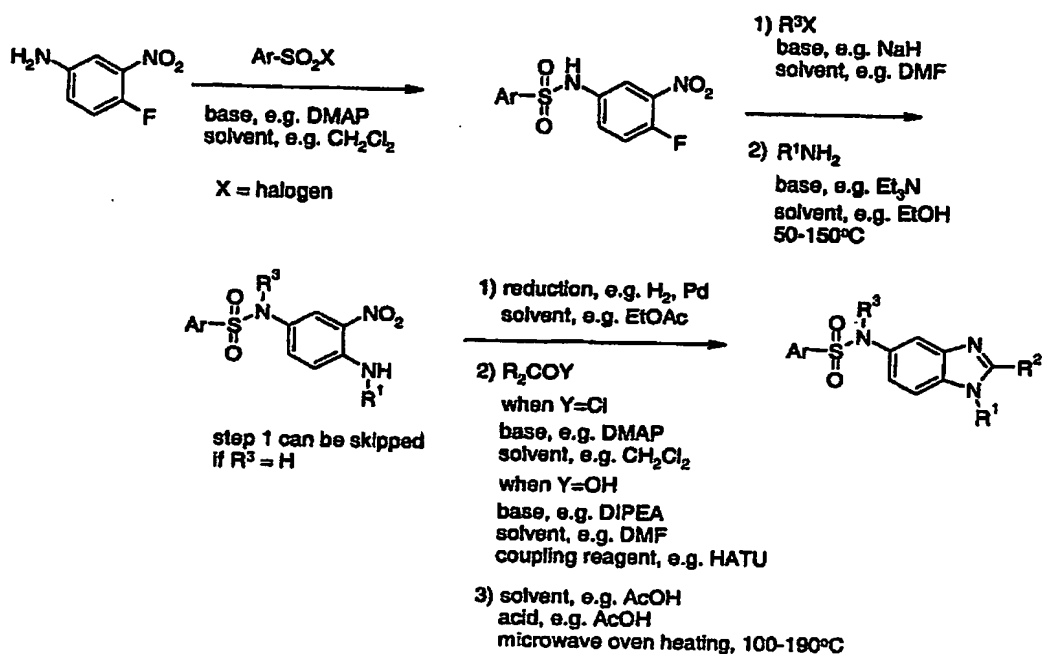
20  $R^3$  is selected from -H,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl, and  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl; and

Ar is selected from  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl, wherein said  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl are optionally substituted with one or more groups selected from  $C_{1-3}$ alkyl, methoxy and halogen.

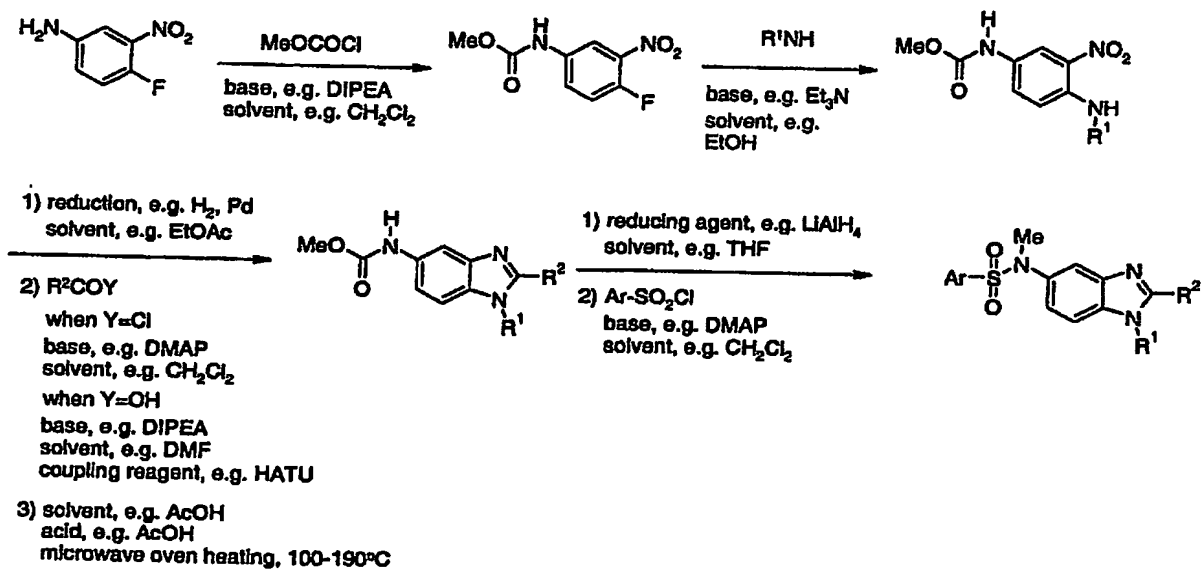
25

Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1-3.

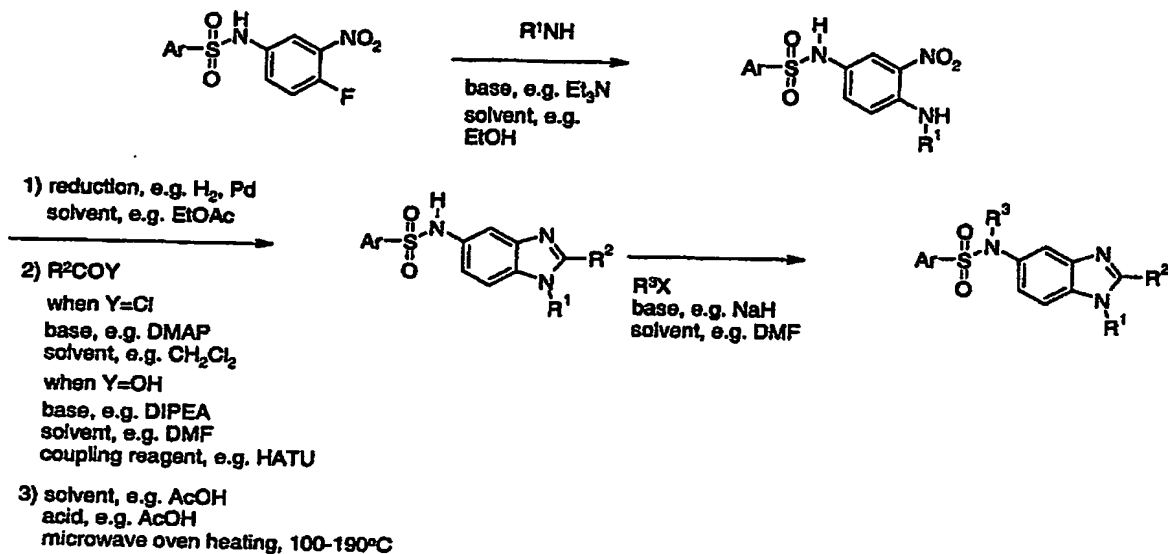
## Scheme 1



## Scheme 2

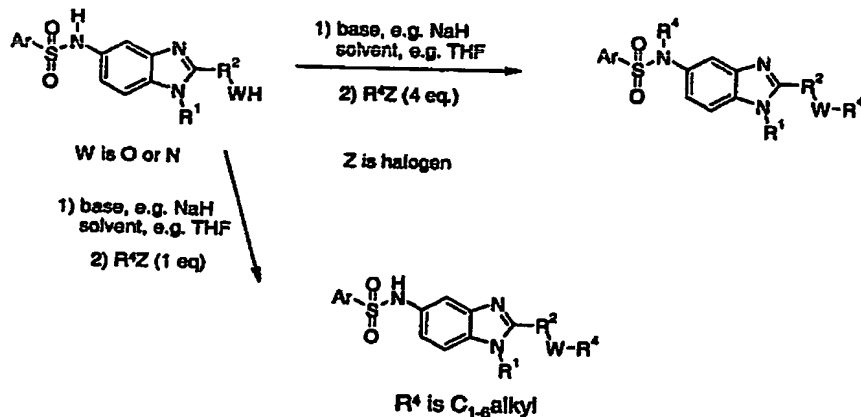


Scheme 3



Ar,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in the specifications.

Scheme 4



$R^1$ ,  $R^2$ , and Ar are as defined in the specifications.

## 5 Biological Evaluation

### hCB<sub>1</sub> and hCB<sub>2</sub> receptor binding

Human CB<sub>1</sub> receptor from Receptor Biology (hCB1) or human CB<sub>2</sub> receptor from BioSignal (hCB2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM  $MgCl_2$ , and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The

IC<sub>50</sub> of the compounds of the invention at hCB<sub>1</sub> and hCB<sub>2</sub> are evaluated from 10-point dose-response curves done with <sup>3</sup>H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl<sub>2</sub>, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

#### hCB<sub>1</sub> and hCB<sub>2</sub> GTPγS binding

Human CB<sub>1</sub> receptor from Receptor Biology (hCB<sub>1</sub>) or human CB<sub>2</sub> receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl<sub>2</sub>, pH 7.4, 0.1% BSA). The EC<sub>50</sub> and E<sub>max</sub> of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPγ<sup>35</sup>S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB<sub>2</sub>) or 10 µM (hCB<sub>1</sub>) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB<sub>2</sub>) or 112.5 µM (hCB<sub>1</sub>) GDP prior to distribution in plates (15 µM (hCB<sub>2</sub>) or 30 µM (hCB<sub>1</sub>) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM MgCl<sub>2</sub>, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (K<sub>i</sub>) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$K_i = IC_{50}/(1+[rad]/K_d),$$

Wherein  $IC_{50}$  is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

$K_d$  is the dissociation constant of the radioactive ligand towards the particular receptor.

Using the above-mentioned assays, the  $K_i$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of 1.7-2681 nM. The  $K_i$  towards human  $CB_2$  receptors for most compounds of the invention is measured to be in the range of about 0.5-22.2 nM. The  $EC_{50}$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of about 4.7-2771.6 nM. The  $E_{max}$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of about 22.3-113%.

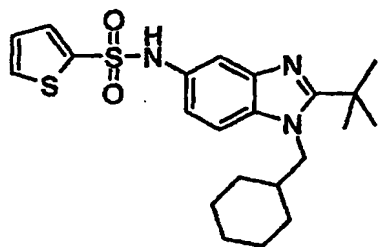
In a particular embodiment, the  $K_i$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of 1.7-50 nM. The  $K_i$  towards human  $CB_2$  receptors for most compounds of the invention is measured to be in the range of about 0.5-15 nM. The  $EC_{50}$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of about 4.7-100 nM. The  $E_{max}$  towards human  $CB_1$  receptors for most compounds of the invention is measured to be in the range of about 60-113%.

### EXAMPLES

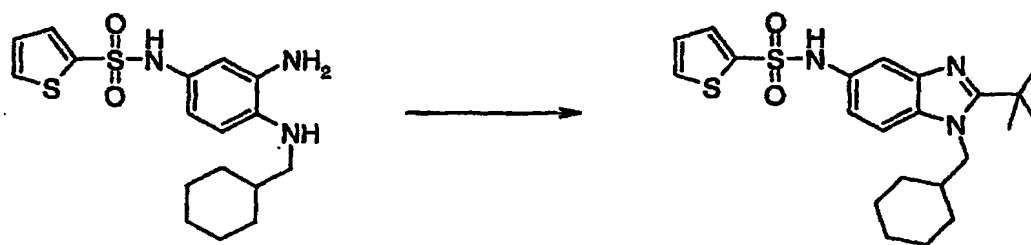
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

#### Example 1

*N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide



**Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide**



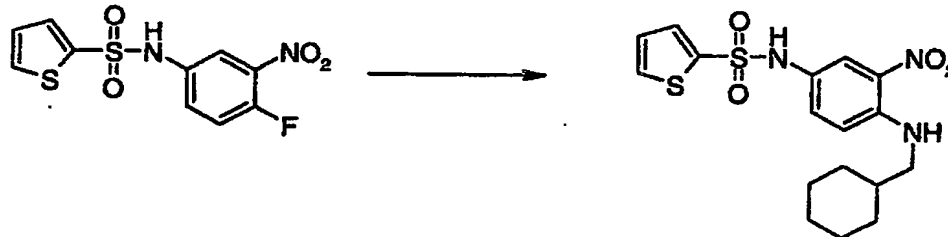
- 5 *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)thiophene-2-sulfonamide (55 mg, 0.150 mmol) (for preparation, see the following steps B, C and D) was dissolved in 3 mL of 1,2-dichloroethane containing TEA (0.030 mL, 0.225 mmol). Trimethylacetyl chloride (0.020 mL, 0.165 mmol) was added dropwise and the solution was stirred at rt for 1h. Glacial AcOH (1 mL) and a few drops of concentrated HCl were added and
- 10 the solution was stirred at 80°C overnight. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 2M NaOH aqueous solution, brine and dried over anhydrous MgSO<sub>4</sub>. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 10 mg (15%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>)
- 15 δ 1.19 (m, 5 H), 1.57 (m, 1 H), 1.59 (m, 1 H), 1.61 (s, 9 H), 1.66 (m, 1 H), 1.73 (m, 2 H), 2.05 (m, 1 H), 4.37 (d, *J*=7.62 Hz, 2 H), 7.02 (dd, *J*=4.98, 3.81 Hz, 1 H), 7.25 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.52 (dd, *J*=3.71, 1.37 Hz, 1 H), 7.66 (d, *J*=2.15 Hz, 1 H), 7.69 (dd, *J*=5.08, 1.37 Hz, 1 H), 7.76 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)<sup>+</sup> 432.1; Anal. Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> + 1.4 TFA + 0.6 H<sub>2</sub>O: C, 49.48; H, 5.29; N, 6.98. Found: C,
- 20 49.47; H, 5.36; N, 6.83.

**Step B. *N*-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide**



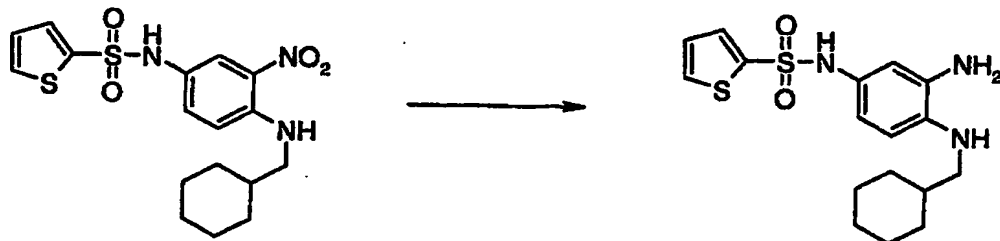
4-Fluoro-3-nitroaniline (1.00 g, 6.41 mmol) and 2-thiophenesulfonyl chloride (1.75 g, 9.62 mmol) were stirred in dichloromethane (150 mL) containing DMAP (1.17g, 9.62 mmol) at rt for 24 h. The solution was washed with 5% KHSO<sub>4</sub> aqueous solution, saturated NaHCO<sub>3</sub> aqueous solution, brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 425 mg (22%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 6.90 (m, 1H), 7.08 (dd, J = 5.08, 3.91 Hz, 1H), 7.26 (t, J = 10.35 Hz, 1H), 7.49 (m, 1H), 7.56 (dd, J = 3.71, 1.37 Hz, 1H), 7.63 (dd, J = 5.08, 1.37 Hz, 1H), 7.78 (dd, J = 6.35, 2.83Hz, 1H).

**Step C. N-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}thiophene-2-sulfonamide**



N-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide (73 mg, 0.241 mmol) and cyclohexylmethyl amine (0.040 mL, 0.289 mmol) were stirred in 3 mL of EtOH containing TEA (0.050 mL, 0.361 mmol) at 75°C for 6h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO<sub>4</sub> solution, saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica gel. Yield: 60 mg (63%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 1.03 (m, 2H), 1.26 (m, 3H), 1.61 (m, 2H), 1.76 (m, 2H), 1.82 (m, 4H), 3.13 (dd, J = 6.64, 5.47Hz, 2H), 6.46 (m, 1H), 6.82 (d, J = 9.18Hz, 1H), 7.05 (dd, J = 4.98, 3.81Hz, 1H), 7.40 (dd, J = 9.18, 2.54Hz, 1H), 7.47 (dd, J = 3.71, 1.37Hz, 1H), 7.59 (dd, J = 5.08, 1.37Hz, 1H), 7.73 (d, J = 2.73Hz, 1H), 8.17 (m, 1H).

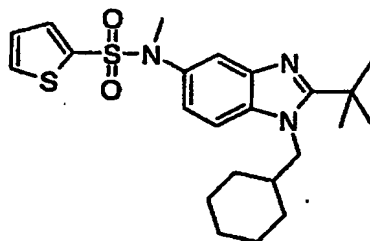
**Step D. *N*-{3-Amino-4-[(cyclohexylmethyl)amino]phenyl}thiophene-2-sulfonamide**



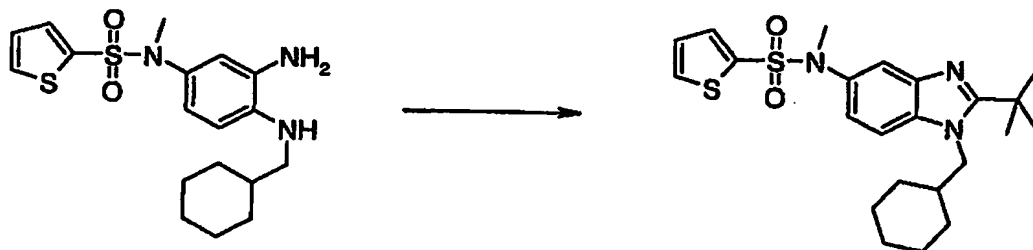
*N*-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}thiophene-2-sulfonamide (60 mg, 0.152 mmol) was dissolved in 5 mL of DMF under nitrogen. Tin (II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt for 6h. More tin(II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt overnight. The reaction mixture was quenched by addition of saturated NaHCO<sub>3</sub> solution at 0°C. The solution was then extracted (2X) with EtOAc and washed with brine and dried over anhydrous MgSO<sub>4</sub>. The product was used directly for Step A without further purification. Yield: 55 mg (99%); MS (ESI) (M+H)<sup>+</sup> 366.14.

### Example 2

15 ***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide**



**Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide**





Following the procedure for Step A in Example 1, using *N*-{3-amino-4-[(cyclohexylmethyl) amino]phenyl} -*N*-methylthiophene-2-sulfonamide (115 mg, 0.303 mmol) (for preparation, see the following steps B, C and D) and trimethylacetyl chloride (0.041 mL, 0.333 mmol) in 3mL of DCE. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 65 mg (38%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.22 (m, 5 H), 1.61 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 2.08 (m, 1 H), 3.29 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.15 (dd, J=5.08, 3.71 Hz, 1 H), 7.33 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 (dd, J=3.71, 1.37 Hz, 1 H), 7.55 (d, J=1.56 Hz, 1 H), 7.81 (dd, J=5.08, 1.37 Hz, 1 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)<sup>+</sup> 446.1; Anal. Calcd for C<sub>23</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> + 1.5 TFA + 0.1 H<sub>2</sub>O: C, 50.49; H, 5.33; N, 6.79. Found: C, 50.55; H, 5.39; N, 6.76.

**Step B. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide**



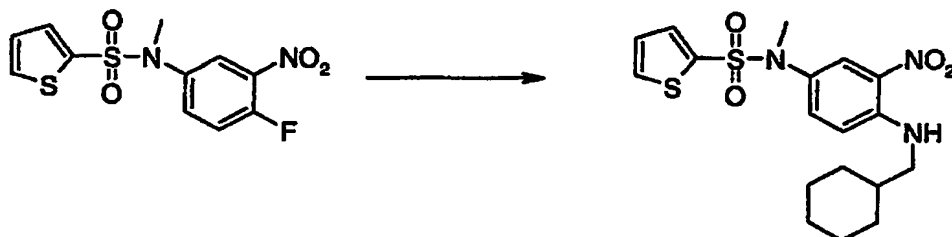
15

A solution of *N*-(4-fluoro-3-nitrophenyl)thiophene-2-sulfonamide (100 mg, 0.331 mmol) in MDF (1 mL) was added to a cold (0°C) stirring DMF solution (2 mL) of NaH (60% dispersion in oil) (20 mg, 0.496 mmol) under nitrogen. The solution was stirred at 0°C for 20 min. Methyl iodide (0.060 mL, 0.993 mmol) was added dropwise and the solution stirred at rt for 3h. The reaction mixture was quenched at 0°C by the slow addition of saturated NH<sub>4</sub>Cl solution. The solvent was evaporated *in vacuo*. The crude product was dissolved in EtOAc and washed with saturated NaHCO<sub>3</sub> aqueous solution, brine and dried over anhydrous MgSO<sub>4</sub>. The product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 78 mg (74%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 3.22 (s, 3H), 7.10 (dd, J = 4.98, 3.81Hz, 1H), 7.26 (dd, J= 3.91, 1.37Hz, 1H), 7.56 (m, 1H), 7.63 (dd, J = 5.08, 1.37Hz, 1H), 7.69 (dd, J = 6.44, 2.73Hz, 1H).

25

**Step C. *N*-{4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}-*N*-methylthiophene-2-sulfonamide**

30

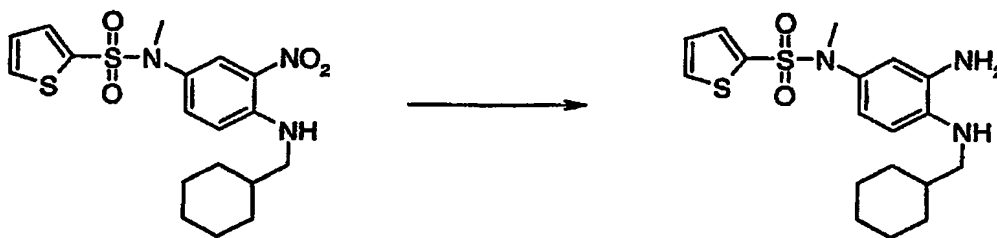


Following the procedure for Step C in Example 1, using *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide (3) (100 mg, 0.316 mmol),

methylcyclohexylamine (0.050 mL, 0.379 mmol) and TEA (0.050 mL, 0.474 mmol) in

5 3 mL of EtOH. The product was used directly for the next step without any column chromatography purification. Yield: 130 mg (99%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 0.98 (m, 1H), 1.04 (m, 1H), 1.20 (m, 1H), 1.66 (m, 2H), 1.75 (m, 2H), 1.81 (d, J = 12.50 Hz, 2H), 3.12 (m, 2H), 3.16 (s, 3H), 6.80 (d, J = 9.37 Hz, 1H), 7.09 (dd, J = 4.98, 3.81 Hz, 1H), 7.37 (dd, J = 3.81, 1.27 Hz, 1H), 7.42 (dd, J = 9.28, 2.64 Hz, 1H), 7.59 (dd, J = 4.98, 1.27 Hz, 1H), 7.65 (d, J = 2.54 Hz, 1H), 8.20 (m, 1H).

**Step D. *N*-{3-Amino-4-[(cyclohexylmethyl)amino]phenyl}-*N*-methylthiophene-2-sulfonamide**

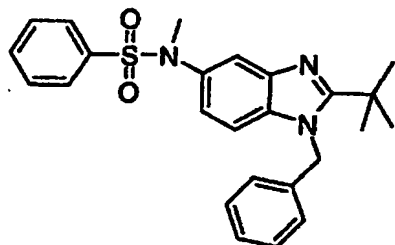


15 Following the procedure for Step D in Example 1, using *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}-*N*-methylthiophene-2-sulfonamide (125 mg, 0.305 mmol) and tin(II) chloride dihydrate (2X345 mg, 2X1.52 mmol). The product was used directly for Step A without further purification. Yield: 115 mg

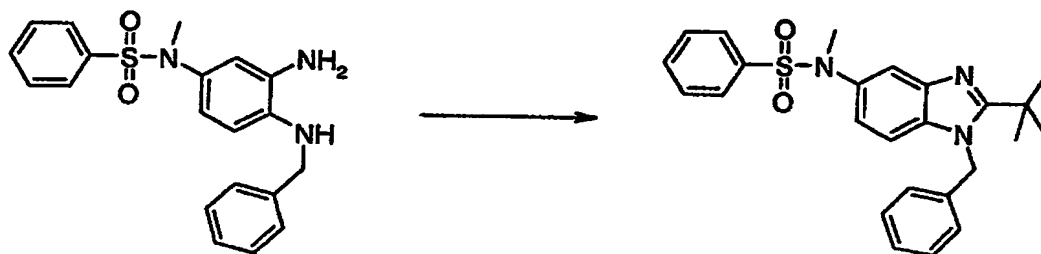
20 (99%); MS (ESI) (M+H)<sup>+</sup> 379.97.

### Example 3

***N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide**



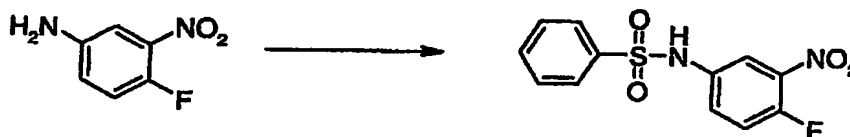
**Step A. *N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide**



- 5 Following the procedure for Step A in Example 1, using *N*-[3-amino-4-[(cyclohexylmethyl)amino]phenyl] -*N*-methylbenzenesulfonamide (88mg, 0.239mmol), trimethylacetyl chloride (0.032mL, 0.262mmol) and DMAP (7.0mg, 0.060mmol) in 5 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title
- 10 compound as the corresponding TFA salt. Yield: 38 mg (29%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.62 (s, 9 H), 3.21 (s, 3 H), 5.93 (s, 2 H), 7.09 (m, 2 H), 7.12 (dd, J=8.98, 2.15 Hz, 1 H), 7.32 (m, 4 H), 7.48 (m, 4 H), 7.57 (dd, J=1.95, 0.59 Hz, 1 H), 7.62 (m, 1 H); MS (ESI) (M+H)<sup>+</sup> 434.1; Anal. Calcd for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + 1.4 TFA + 0.2 H<sub>2</sub>O: C, 55.95; H, 4.86; N, 7.04. Found: C, 55.90; H, 4.85; N, 7.06.

15

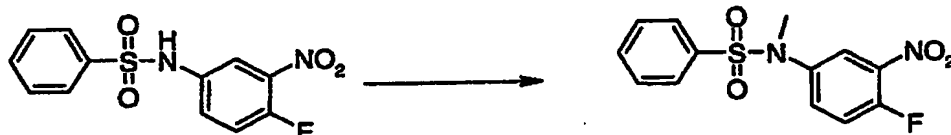
**Step B. *N*-(4-Fluoro-3-nitrophenyl)benzenesulfonamide**



- 20 4-Fluoro-3-nitroaniline (2.00 g, 12.8 mmol) was dissolved in 50 mL of pyridine containing a catalytic amount of DMAP. Benzenesulfonyl chloride (1.96 mL, 15.36 mmol) was added and the solution was stirred at rt for 3h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO<sub>4</sub> solution, saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica

gel. Yield: 3.40 g (90%);  $^1\text{H}$  NMR (400 MHz, CHLOROFORM-D)  $\delta$  7.09 (m, 1H), 7.18 (dd,  $J$  = 9.96, 8.98 Hz, 1H), 7.40 (m, 1H), 7.48 (m, 2H), 7.58 (m, 1H), 7.71 (dd,  $J$  = 6.25, 2.73 Hz, 1H), 7.76 (m, 2H).

5 **Step C. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide**



Following the procedure for Step B in Example 2, using *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (1.00 g, 3.38 mmol), NaH (60% dispersion in oil) (160 mg, 4.06 mmol) and methyl iodide (0.315 mL, 5.07 mmol) in 25 mL of DMF.

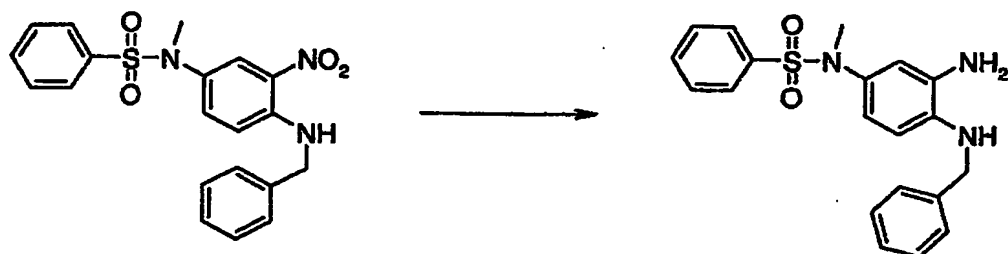
- 10 The product was purified by flash chromatography using dichloromethane as eluent on silica gel. Yield: 815 mg (78%);  $^1\text{H}$  NMR (400 MHz, CHLOROFORM-D)  $\delta$  3.19 (s, 3H), 7.28 (m, 1H), 7.51 (m, 1H), 7.54 (m, 2H), 7.57 (m, 1H), 7.65 (m, 2H).

**Step D. *N*-[4-(Benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide**



- 15 Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzene sulfonamide (71 mg, 0.229 mmol, benzylamine (0.030 mL, 0.275 mmol) and TEA (0.050 mL, 0.344 mmol) in 3 mL of EtOH. The product was used directly for the next step without further purification. Yield: 99 mg (99%);  $^1\text{H}$  NMR (400 MHz, CHLOROFORM-D)  $\delta$  3.12 (s, 3H), 4.56 (d,  $J$  = 5.47 Hz, 2H), 6.81 (d,  $J$  = 9.18 Hz, 1H), 7.34 (m, 3H), 7.40 (m, 3H), 7.49 (m, 2H), 7.57 (m, 1H), 7.60 (m, 1H), 7.64 (dd,  $J$  = 4.30, 1.95 Hz, 1H), 8.47 (m, 1H).

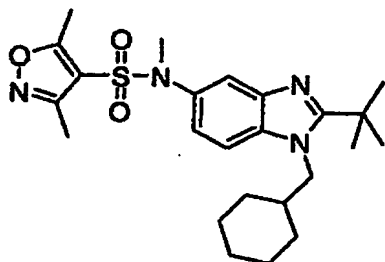
- 25 **Step E. *N*-[3-Amino-4-[(cyclohexylmethyl)amino]phenyl]-*N*-methylbenzenesulfonamide**



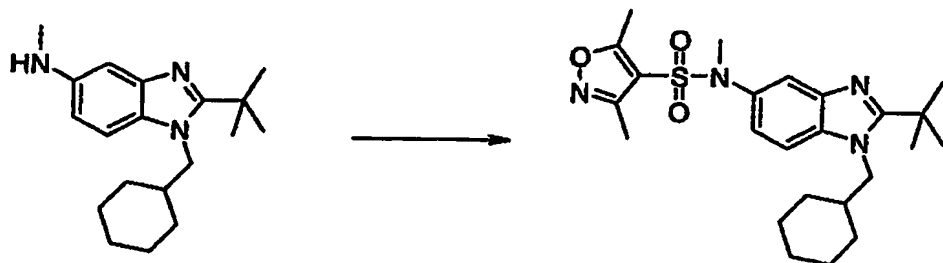
*N*-[4-(benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide (95 mg, 0.239 mmol) was dissolved in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H<sub>2</sub> atmosphere (40 psi) at rt for 4h. The solution was filtered through Celite and the solvent was evaporated. The product was used directly for Step A without further purification. Yield: 88 mg (99%); MS (ESI) (M+H)<sup>+</sup> 367.97.

#### Example 4

10 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide



Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide



2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (35 mg, 0.117 mmol) (for preparation, see the following steps B, C, D, E and F) and 3,5-dimethylisoxazole-4-sulfonyl chloride (0.030 mg, 0.140 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The

solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (73%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.21 (m, 5 H), 1.58 (m, 2 H), 1.65 (s, 10 H), 1.74 (m, 2 H), 1.88 (s, 3 H), 2.08 (m, 1 H), 2.33 (s, 3 H), 3.31 (s, 3 H), 4.46 (d, J=7.81 Hz, 2 H), 7.47 (dd, J=8.98, 1.95 Hz, 1 H), 7.68 (d, J=1.76 Hz, 1 H), 7.91 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)<sup>+</sup> 459.2; Anal. Calcd for C<sub>24</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>S + 1.6 TFA + 0.2 H<sub>2</sub>O: C, 50.68; H, 5.63; N, 8.69. Found: C, 50.70; H, 5.65; N, 8.81.

10 **Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate**

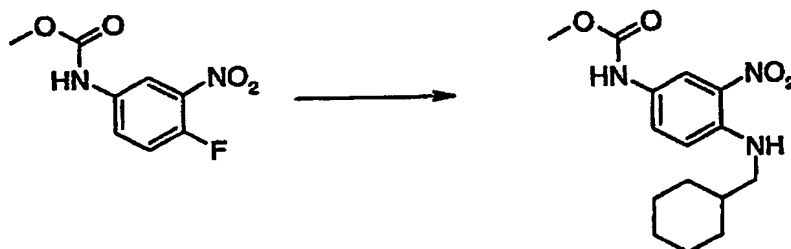


Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight.

15 The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO<sub>4</sub>. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3 H), 7.02 (s, 1 H), 7.23 (m, 1 H), 7.72 (d, J=8.59 Hz, 1 H), 8.17 (dd, J=6.35, 2.64 Hz, 1 H).

20

**Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate**

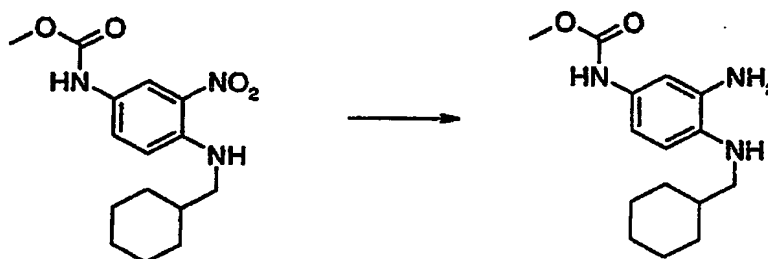


Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO<sub>4</sub> solution, saturated NaHCO<sub>3</sub>

25

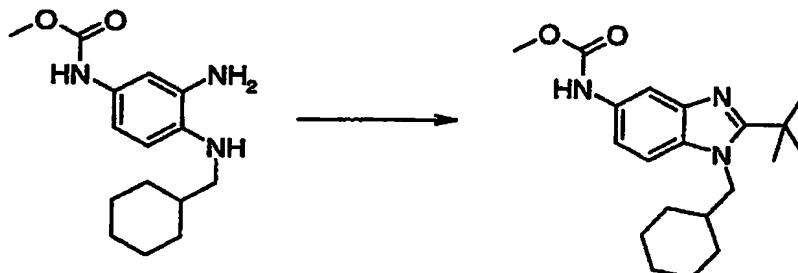
solution, brine and dried over anhydrous  $\text{MgSO}_4$ . The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%);  $^1\text{H}$  NMR (400 MHz,  $\text{CHLOROFORM-D}$ )  $\delta$  1.04 (ddd,  $J = 24.02, 12.11, 2.93\text{Hz}$ , 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd,  $J = 6.44, 5.66\text{Hz}$ , 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d,  $J = 9.37\text{ Hz}$ , 1H), 7.63 (m, 1H), 8.05 (d,  $J = 2.54\text{ Hz}$ , 1H), 8.09 (m, 1H).

**Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate**



Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under  $\text{H}_2$  atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent was evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%). MS (ESI)  $(\text{M}+\text{H})^+$  277.9.

**Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1H-benzimidazol-5-yl]carbamate**



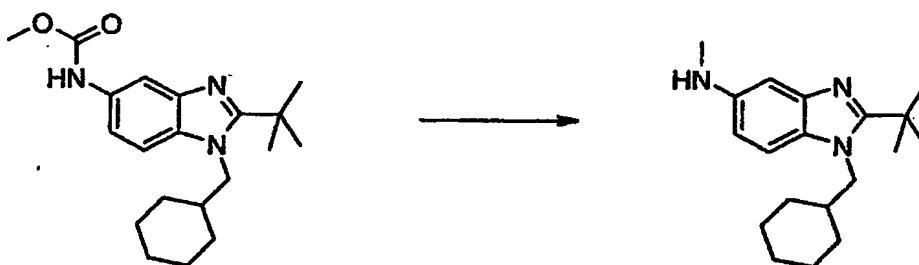
Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The

residue was divided in two portions and each of them was dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The contents of the two tubes were combined and the solvent was

5 evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s,

10 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

**Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine**



15 Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution was stirred at 0°C for 15min. LiAlH<sub>4</sub> (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of

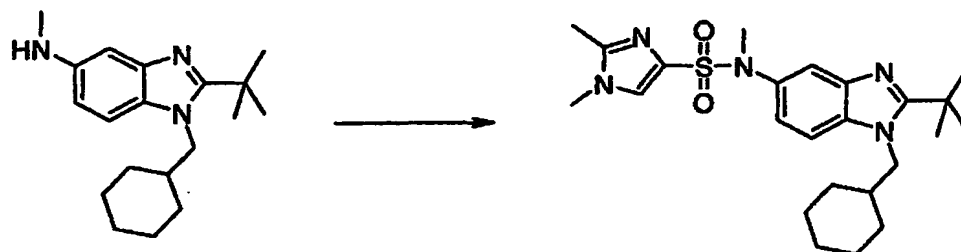
20 MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 (s, 2 H) 1.17 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 2 H) 1.67 (m, 2 H) 1.72 (m, 2

25 H) 2.02 (m, 1 H) 2.87 (s, 3 H) 4.06 (d, J=7.62 Hz, 2 H) 6.60 (dd, J=8.69, 2.25 Hz, 1 H) 7.00 (d, J=1.76 Hz, 1 H) 7.12 (d, J=8.59 Hz, 1 H).



**Example 5**

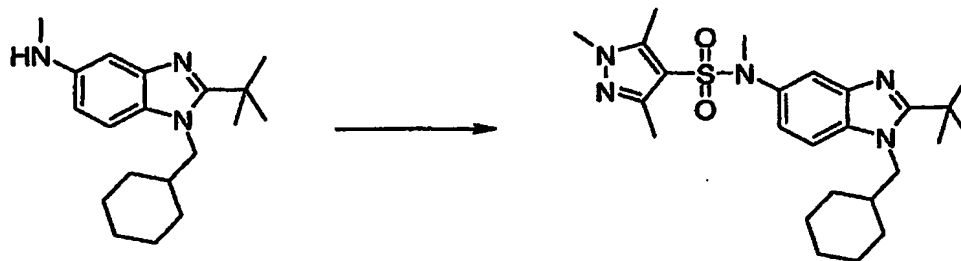
***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-4-sulfonamide**



- 5 Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,2-dimethyl-1*H*-imidazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP (catalytic) in 3 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound
- 10 as the corresponding TFA salt. Yield: 47 mg (69%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.22 (m, 5 H), 1.62 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.09 (m, 1 H), 2.34 (s, 3 H), 3.28 (s, 3 H), 3.61 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.43 (dd, J=8.98, 2.15 Hz, 1 H), 7.51 (s, 1 H), 7.66 (d, J=1.95 Hz, 1 H), 7.82 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)<sup>+</sup> 458.2; Anal. Calcd for C<sub>24</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>S + 1.7 TFA +
- 15 0.1 H<sub>2</sub>O: C, 50.38; H, 5.69; N, 10.72. Found: C, 50.39; H, 5.73; N, 10.73.

**Example 6**

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,3,5-tetramethyl-1*H*-pyrazole-4-sulfonamide**



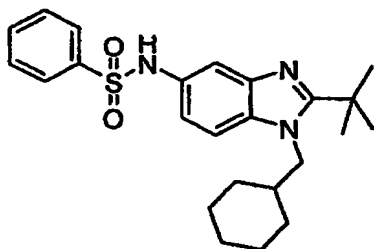
20

Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP

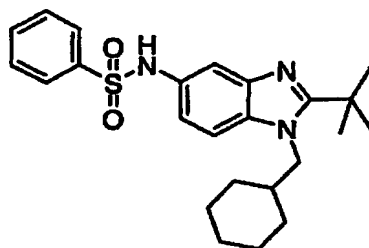
(catalytic) in 3mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (70%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.20 (m, 5 H), 1.56 (m, 2 H), 1.65 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 1.80 (s, 3 H), 2.08 (m, 1 H), 2.16 (s, 3 H), 3.21 (s, 3 H), 3.69 (s, 3 H), 4.44 (d, J=7.81 Hz, 2 H), 7.38 (dd, J=9.08, 2.05 Hz, 1 H), 7.62 (d, J=1.56 Hz, 1 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)<sup>+</sup> 472.2; Anal. Calcd for C<sub>25</sub>H<sub>37</sub>N<sub>5</sub>O<sub>2</sub>S + 1.2 TFA + 0.4 H<sub>2</sub>O: C, 53.45; H, 6.38; N, 11.37. Found: C, 53.50; H, 6.38; N, 11.29.

### 10 Example 7

*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide



**Step A.** *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide



15

DMAP (44.0 mg, 0.36 mmol) and then trimethylacetyl chloride (199.0 mg, 1.65 mmol) at 0 °C was added into a solution of *N*-[3-amino-4-[(cyclohexylmethyl)amino]phenyl]benzene sulfonamide (540.1 mg, 1.5 mmol) (for preparation, see the following steps B, C and D) in dichloromethane (40 mL). The mixture was stirred for 5 h at room temperature. After evaporation of the solvent, the residue was dissolved in 1,2-dichloroethane (5x5 mL) in five Teflon-capped test tubes. The vessels were irradiated by microwave for 2h at 170 °C. The combined reaction mixture diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (10 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation, the residue

20

was purified by MPLC (hex/EtOAc 1:1 on silica gel) to give 568.2 mg (89%) of a white solid as the title compound. Part of the product was converted to TFA salt.

<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.18 (m, 5 H), 1.55 (m, 2 H), 1.59 (s, 9 H), 1.65 (m, 1 H), 1.71 (m, 2 H), 2.03 (m, 1 H), 4.34 (d, J=7.42 Hz, 2 H), 7.20 (d, J=9.18 Hz, 1 H), 7.44 (m, 2 H), 7.53 (m, 1 H), 7.58 (s, 1 H), 7.70 (d, J=8.79 Hz, 1 H), 7.76 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)<sup>+</sup> = 426.1. Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>S+1.10 TFA+0.10 H<sub>2</sub>O: C, 56.92; H, 5.89; N, 7.60. Found: C, 56.95; H, 5.92; N, 7.56.

**Step B. *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide**

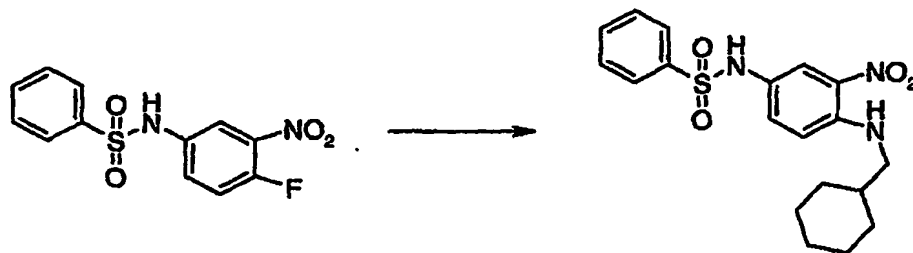


10

Benzenesulfonyl chloride (5.61 mL, 7.74 g, 44 mmol) was added into a solution of 4-fluoro-3-nitro-aniline (6.24 g, 40 mmol) in pyridine (40 mL) at 0 °C. The reaction mixture was stirred for two days at room temperature. Upon evaporation of the solvent, the residue was dissolved in EtOAc (500 mL), washed with water (50 mL), 2N HCl (2x50 mL), water (50 mL), sat. sodium bicarbonate aqueous solution (2x50 mL), sat. sodium chloride aqueous solution (2x50 mL) and dried over sodium sulphate. After filtration and concentration, 12.1 g (100%) of a brown solid was obtained as the title compound. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>Cl): δ 7.20 (m, 2 H), 7.44 (m, 1 H), 7.52 (m, 2 H), 7.61 (m, 1 H), 7.75 (dd, J=6.25, 2.73 Hz, 1 H), 7.81 (m, 2 H).

20

**Step C: *N*-[4-[(cyclohexylmethyl)amino]-3-nitrophenyl]benzenesulfonamide**

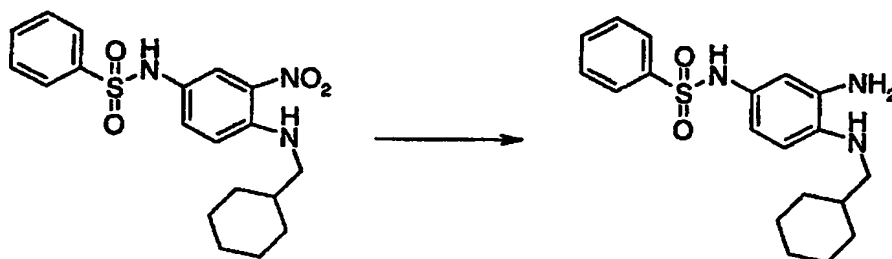


Cyclohexylmethylamine (3.48 mL, 3.03 g, 26.7 mmol ) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (3.60 g, 12.1 mmol) in 60 mL of EtOH-H<sub>2</sub>O (1:1 V/V) at room temperature. The reaction mixture was heated for 48 h at 60 °C, and allowed to cool to room temperature and concentrated to a small volume, and

25

then extracted with EtOAc. The crude product was purified by MPLC using Hex/EtOAc (4:1) on silica gel to give 3.75 g (79%) of an orang-red solid as the title compound. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>Cl): δ 1.05 (m, 2 H), 1.24 (m, 3 H), 1.72 (m, 6 H), 3.12 (dd, *J*=6.64, 5.47 Hz, 2 H), 6.23 (s, 1 H), 6.79 (d, *J*=9.18 Hz, 1 H), 7.36 (dd, *J*=9.08, 2.64 Hz, 1 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 7.63 (d, *J*=2.54 Hz, 1 H), 7.72 (m, 2 H), 8.14 (s, 1 H).

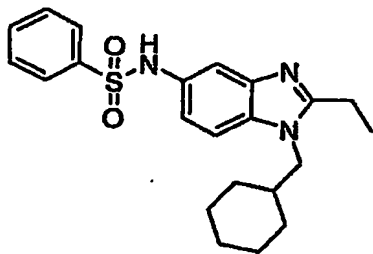
**Step D: *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzenesulfonamide**



*N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}benzenesulfonamide (3.75 g, 9.63 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.5 g) at 30-40 psi H<sub>2</sub> in Parr shaker for 20 h at room temperature. After filtration through Celite and concentration, 4.0 g (100%) of a light yellow solid was obtained as the title compound, which was used for Step A without further purification. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>Cl): δ 0.88 (m, 1 H), 0.99 (m, 2 H), 1.23 (m, 3 H), 1.56 (m, 1 H), 1.75 (m, 4 H), 2.86 (d, *J*=6.64 Hz, 2 H), 3.33 (s broad, 3 H), 6.30 (s broad, 1 H), 6.33 (dd, *J*=8.30, 2.44 Hz, 1 H), 6.41 (m, 1 H), 6.56 (d, *J*=2.34 Hz, 1 H), 7.41 (m, 2 H) 7.52 (m, 1 H), 7.70 (m, 2 H). MS (ESI) (*M*-H)<sup>+</sup>: 359.89.

**Example 8**

***N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide**



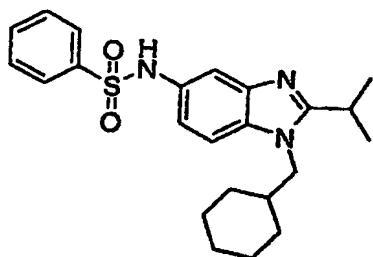
Following the procedure for Step A in Example 7, using a solution *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.5 mmol) and

DMAP (15.0 mg, 0.12 mmol) in dichloromethane (15 mL), to which was added propionyl chloride (50.9 mg, 0.55 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature. The crude product was purified by MPLC (hex/EtOAc 1:9 on silica gel) to give 157.7 mg (79%) of a white solid as the title compound. Part of the product was converted to TFA salt. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.12 (m, 2 H), 1.21 (m, 3 H), 1.48 (t, J=7.62 Hz, 3 H), 1.60 (m, 2 H), 1.68 (m, 1 H), 1.73 (m, 2 H), 1.90 (m, 1 H), 3.18 (q, J=7.49 Hz, 2 H), 4.19 (d, J=7.62 Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.71 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H). MS (ESI) (M+H)<sup>+</sup> = 398.1

10

**Example 9**

*N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzene sulfonamide



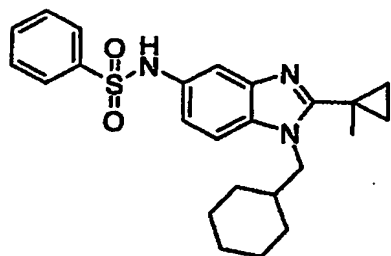
Following the procedure for Step A in Example 7, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (182.1 mg, 0.5 mmol), DMAP (15.0 mg, 0.12 mmol) and isobutyryl chloride (50.2 mg, 0.56 mmol) CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The crude product was purified by MPLC (Hex/EtOAc 1:1). Yield: 178.4 mg (86%). <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.17 (m, 5 H), 1.47 (d, J=6.83 Hz, 6 H), 1.60 (m, 2 H), 1.72 (m, 3 H), 1.88 (m, 1 H), 3.62 (m, 1 H), 4.25 (d, J=7.62 Hz, 2 H), 7.25 (dd, J=8.88, 2.05 Hz, 1 H), 7.48 (m, 2 H), 7.57 (m, 2 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)<sup>+</sup> = 412.1.

20

**Example 10**

*N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide

25

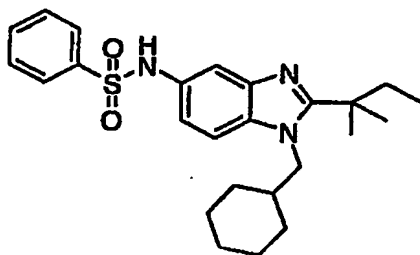


Diisopropylethylamine (104.7 mg, 0.81 mmol) was added into a solution of *N*-[3-amino-4-[(cyclohexylmethyl)amino]phenyl]benzenesulfonamide (195.6 mg, 0.543 mmol), and 1-methylcyclopropanecarboxylic acid (59.8 mg, 0.6 mmol) in DMF (5 mL) at 0 °C. Stirring for 20 min. HATU (246.4 mg, 0.65 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (10 mL) and heated for 20 h at 80 °C. Upon evaporation of the solvent, 93.7 mg of the acetate salt was lyophilized, and the rest was diluted with EtOAc (100 mL), washed with 2N NaOH (10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, 144.9 mg of the free amine as the title compound was obtained. Total yield: 99%. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 0.89 (m, 2 H), 1.10 (m, 4 H), 1.21 (m, 3 H), 1.45 (s, 3 H), 1.55 (d, 2 H), 1.69 (m, 3H), 2.08 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 7.01 (dd, J=8.79, 1.95 Hz, 1 H,) 7.25 (d, J=1.95 Hz, 1 H), 7.35 (d, J=8.79 Hz, 1 H), 7.40 (t, J=7.62 Hz, 2 H), 7.50 (t, J=7.42 Hz, 1 H), 7.68 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)<sup>+</sup> = 424.1. Anal. Calcd for C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S+0.4 AcOH+0.10 H<sub>2</sub>O: C, 65.92; H, 6.98; N, 9.45. Found: C, 66.01; H, 6.89; N, 9.09.

20

**Example 11**

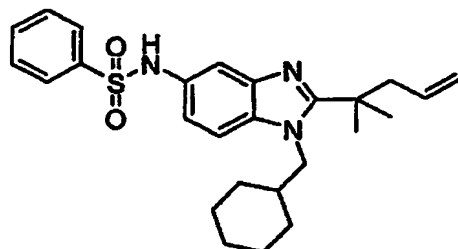
***N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



Following the procedure in Example 10, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-dimethylbutyric acid (63.9 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by reversed HPLC using 30-80% CH<sub>3</sub>CN/H<sub>2</sub>O to give 39.9 mg (14%) of a white solid as the title compound. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 0.81 (t, J=7.52 Hz, 3 H), 1.20 (m, 5 H), 1.58 (m, 2 H), 1.62 (s, 6 H), 1.68 (m, 1 H), 1.75 (m, 2 H), 1.97 (q, J=7.62 Hz, 2 H), 2.03 (m, 1 H), 4.37 (d, J=7.62 Hz, 2 H), 7.23 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (m, 1 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)<sup>+</sup> = 440.2. Anal. Calcd for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>S+1.0 TFA+0.60 H<sub>2</sub>O: C, 57.45; H, 6.29; N, 7.44. Found: C, 57.49; H, 6.39; N, 7.35.

### Example 12

*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethyl-3-butenyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide

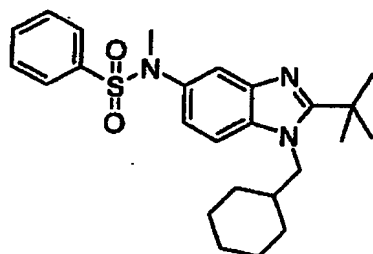


Following the procedure in Example 10, using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-dimethyl-4-pentenoic acid (70.5 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol) ) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by by reversed HPLC using 30-80% CH<sub>3</sub>CN/H<sub>2</sub>O to give 38.2 mg (14%) of a white solid as the title compound. <sup>1</sup>HNMR (400MHz, CD<sub>3</sub>OD): δ 1.19 (m, 5 H), 1.59 (m, 2 H), 1.65 (s, 6 H), 1.68 (m, 1 H), 1.74 (m, 2 H), 2.04 (m, 1 H), 2.67 (d, J=7.42 Hz, 2 H), 4.40 (d, J=7.62 Hz, 2 H), 5.03 (s, 1 H), 5.07 (m, 1 H), 5.60 (m, 1 H), 7.23 (dd, J=8.98, 2.15 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (d, J=1.56 Hz, 1 H), 7.74 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI)

(M+H)<sup>+</sup> = 452.2. Anal. Calcd for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>S+1.2 TFA: C, 57.97; H, 5.86; N, 7.14. Found: C, 58.00; H, 5.74; N, 7.06.

### Example 13

5 ***N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide**

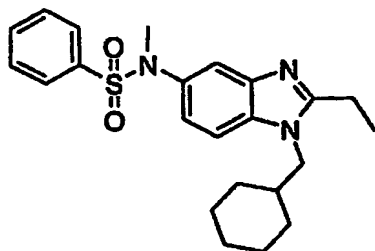


NaH (54.0 mg, 60%, 1.34 mmol) was added to a solution of *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide (258.5 mg, 0.607 mmol) in THF (15 mL) at 0 °C. After stirring for 1h, MeI (259.8 mg, 1.83 mmol) was added. The mixture was stirred overnight at room temperature, quenched with sat. NaHCO<sub>3</sub> (5 mL). The two phases were separated. The aqueous was extracted with EtOAc (3x20 ml). The combined organic phases were washed with NaHCO<sub>3</sub> (2x10 mL) and dried with Na<sub>2</sub>SO<sub>4</sub>. After concentration, the residue was purified by MPLC using hex/EtOAc (1:1) on silica gel to give 216.5 mg (81%) of the title product, and converted to TFA salt as a white solid. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.20 (m, 5 H), 1.60 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 1 H), 3.24 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.26 (dd, J=8.98, 2.15 Hz, 1 H), 7.50 (m, 5 H), 7.65 (m, 1 H), 7.81 (d, J=9.18 Hz, 1 H). MS (ESI) (M+H)<sup>+</sup> = 440.2. Anal. Calcd for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>S+1.20 TFA: C, 57.09; H, 5.98; N, 7.29. Found: C, 57.07; H, 6.01; N, 7.25.

### Example 14

25 ***N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide**



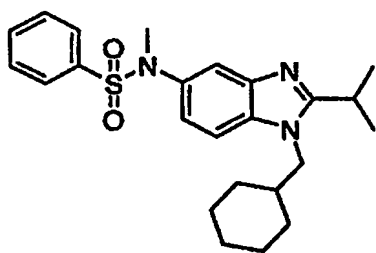


Following the procedure in Example 13, using *N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (91.3 mg, 0.23 mmol), sodium hydride (28.2 mg, 60%, 0.71 mmol) and iodomethane (97.9 mg, 0.69 mmol) in THF(10 mL). Yield: 69.7 mg (74%); white solid for TFA salt. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.20 (m, 5 H), 1.51 (t, J=7.52 Hz, 3 H), 1.65 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.95 (m, 1 H), 3.22 (q, J=7.62 Hz, 2 H), 3.27 (s, 3 H), 4.26 (d, J=7.62 Hz, 2 H), 7.29 (dd, J=8.88, 2.05 Hz, 1 H), 7.50 (d, J=1.95 Hz, 1 H), 7.54 (m, 4 H), 7.67 (m, 1 H), 7.80 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)<sup>+</sup> = 412.1

10

**Example 15**

*N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide

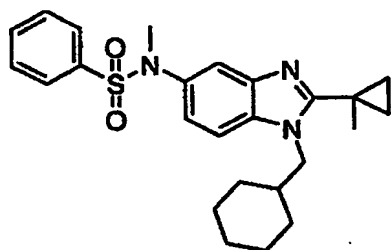


15 Following the procedure in Example 13, using *N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (81.8 mg, 0.199 mmol), sodium hydride (24.0 mg, 60%, 0.596 mmol) and iodomethane (84.7 mg, 0.597 mmol) in THF (15 mL). Yield: 80.1 mg (95%); The title compound was converted to white solid as a TFA salt. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.20 (m, 5 H), 1.51 (d, J=6.83 Hz, 6 H), 1.64 (m, 2 H), 1.69 (m, 1 H), 1.76 (m, 2 H), 1.93 (m, 1 H), 3.27 (s, 3 H), 3.67 (m, 1 H), 4.31 (d, J=7.62 Hz, 2 H), 7.28 (m, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.81 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)<sup>+</sup> = 426.1.

20

**Example 16**

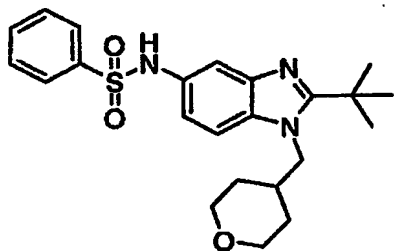
***N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide**



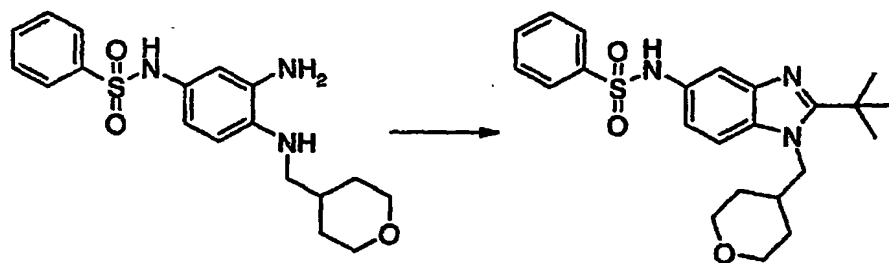
Following the procedure in Example 13, using *N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (144.9 mg, 0.342 mmol), sodium hydride (30.0 mg, 60%, 0.752 mmol) and iodomethane (145.7 mg, 1.03 mmol) in THF (15 mL). Yield: 72.3 mg (48%); compound was converted to a white solid as a TFA salt. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.19 (m, 4 H), 1.26 (m, 3 H), 1.34 (m, 2 H), 1.59 (s, 3 H), 1.71 (m, 5 H), 2.19 (m, 1 H), 3.26 (s, 3 H), 4.38 (d, J=7.81 Hz, 2 H), 7.29 (dd, J=9.08, 2.05 Hz, 1 H), 7.50 (m, 1 H), 7.52 (m, 1 H) 7.55 (m, 3 H), 7.67 (m, 1 H), 7.83 (d, J=8.98 Hz, 1 H). MS (ESI) (M+H)<sup>+</sup> = 438.2. Anal. Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>S+1.2 TFA+0.10 H<sub>2</sub>O: C, 57.11; H, 5.67; N, 7.29. Found: C, 57.19; H, 5.74; N, 7.22.

**Example 17**

***N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide**

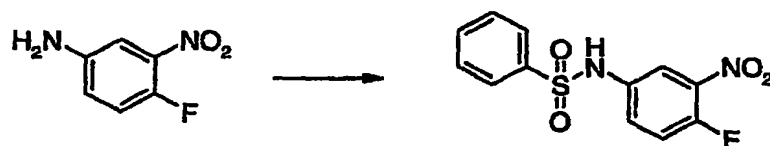


**Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



Catalytic DMAP in one portion and pivaloyl chloride (0.26 mL, 1.1 eq) were added dropwise sequentially to a stirring solution of *N*-[3-amino-4-[(tetrahydro-2*H*-pyran-4-yl)methyl]amino] phenyl]-benzenesulfonamide (705.2 mg, 1.95 mmol) (for preparation, see Steps B, C and D) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $0^\circ\text{C}$ . The solution was stirred for 2 hours, then the solvent was concentrated, and the residue was re-dissolved in AcOH (2 mL). The resulting solution was heated at  $150^\circ\text{C}$  for 1800 s using microwave irradiation and the solvent was then concentrated. The residue was re-dissolved in EtOAc, washed with 1N NaOH (2X) and brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Purification by MPLC using EtOAc followed by reversed-phase HPLC using 10-90% MeCN in  $\text{H}_2\text{O}$  afforded the title compound as a colourless solid (16.3 mg, 2% yield);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.46-1.55 (m, 4 H), 1.62 (s, 9 H), 2.25-2.35 (m, 1 H), 3.30-3.34 (m, 2 H), 3.88-3.92 (m, 2 H), 4.43 (d,  $J=7.42$  Hz, 2 H), 7.22 (dd,  $J=9.08, 2.05$  Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.60 (d,  $J=2.05$  Hz, 1 H), 7.75-7.80 (m, 3 H); MS (ESI)  $(\text{M}+\text{H})^+ = 428.0$ .

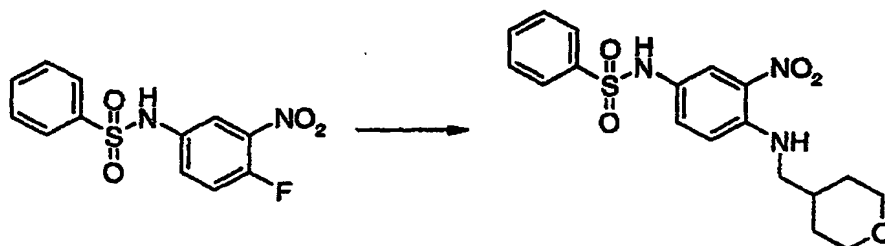
#### Step B. *N*-(4-fluoro-3-nitrophenyl)- benzenesulfonamide



Catalytic DMAP in one portion and benzene sulfonyl chloride (9.82 mL, 1.2 eq) dropwise were added sequentially to a stirring solution of 4-fluoro-3-nitroaniline (10 g, 64.1 mmol) in pyridine (52 mL) at  $0^\circ\text{C}$ . The solution was stirred at  $0^\circ\text{C}$  for 30 minutes and then warmed gradually to room temperature. After 3 hours at room temperature, the solution was diluted with EtOAc (15 mL) and was washed with water until the organic layer contained no pyridine by TLC ( $\text{CH}_2\text{Cl}_2$ ). The solution was dried with anhydrous  $\text{Na}_2\text{SO}_4$ . Purification by MPLC using  $\text{CH}_2\text{Cl}_2$  afforded the

title compound as a pale yellow solid (13.6 g, 71% yield);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (dd,  $J=10.15, 8.98$  Hz, 1 H), 7.32-7.36 (brs, 1 H), 7.44 (m, 1 H), 7.51 (m, 2 H), 7.62 (m, 1 H), 7.77 (dd,  $J=6.25, 2.93$  Hz, 1 H), 7.82 (m, 2 H).

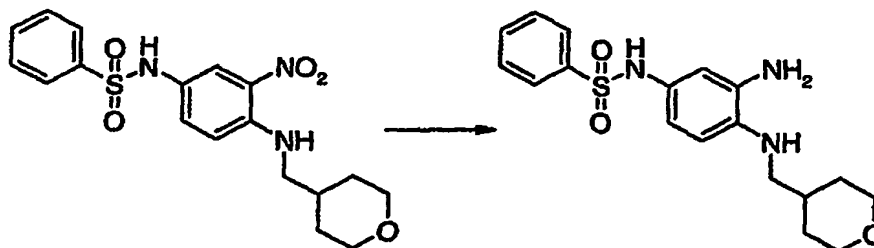
5 **Step C. *N*-[3-nitro-4-[[tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide**



4-Tetrahydropyranmethylaniline (468 mg, 1.2 eq) in EtOH (0.5 mL) was added to a stirring solution of *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol) and triethylamine (0.47 mL, 1 eq) in EtOH: $\text{H}_2\text{O}$  4:1 (15 mL) at room temperature. The solution was heated at  $60^\circ\text{C}$  overnight, then cooled to room temperature. The cooled solution was poured into  $\text{H}_2\text{O}$  and was extracted (3X) with EtOAc. The combined organic phases were washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was purified by MPLC using 1:1 heptane:EtOAc to afford the title compound as a bright red solid (767.5 mg, 58%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41-1.46 (m, 2 H), 1.65-1.75 (m, 2 H), 1.90-1.98 (m, 1 H), 3.18-3.21 (m, 2 H), 3.39-3.45 (m, 2 H), 4.00-4.04 (m, 2 H), 6.61 (s, 1 H), 6.80 (d,  $J=9.18$  Hz, 1 H), 7.38 (dd,  $J=9.28, 2.64$  Hz, 1 H), 7.46-7.50 (m, 2 H), 7.56-7.60 (m, 1 H), 7.69 (d,  $J=2.54$  Hz, 1 H), 7.73-7.75 (m, 2 H), 8.10 (m, 1 H).

20

**Step D. *N*-[3-amino-4-[[tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide**



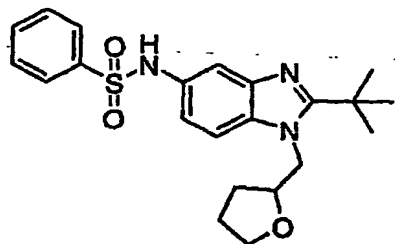
Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[[[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide (767.5 mg, 1.96 mmol) and a catalytic amount of 10% Pd/C in EtOAc (50 mL). LC/MS analysis indicated that the compound was of sufficient purity (>95%) to be used directly for Step A.

- 5 Yield: 705.2 mg, 100%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33-1.44 (m, 2 H), 1.61-1.73 (m, 2 H), 1.81-1.88 (m, 1 H), 2.95 (d, *J*=6.64 Hz, 2 H), 3.37-3.43 (m, 5 H), 3.99 (dd, *J*=10.84, 3.42 Hz, 2 H), 6.27-6.31 (br. s., 1 H), 6.34-6.36 (m, 1 H), 6.42-6.44 (m, 1 H), 6.58 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.55 (m, 1 H), 7.70-7.74 (m, 1 H).

10

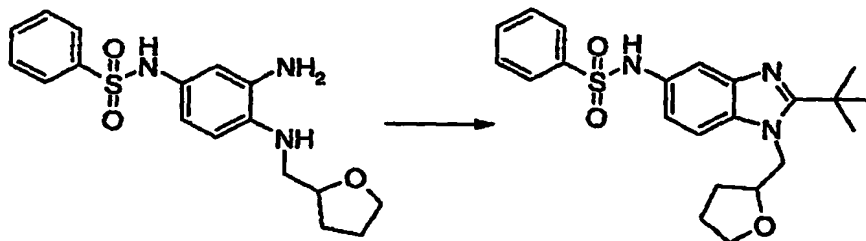
### Example 18

*N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



15

Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



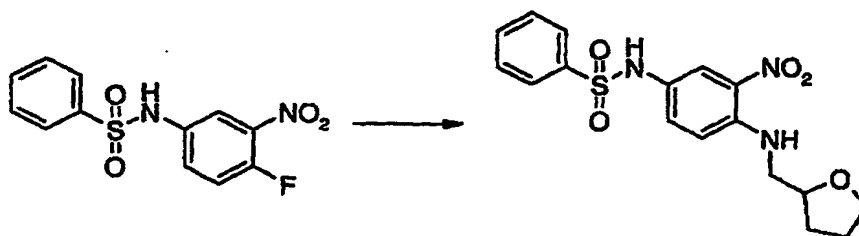
20

Following the procedure for Step A in Example 17, using *N*-[3-amino-4-[[[(tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide (597.2 mg, 1.72 mmol) (for preparation, see the following steps B and C), CH<sub>2</sub>Cl<sub>2</sub> (30 mL), catalytic DMAP and pivaloyl chloride (0.23 mL, 1.1 eq), followed by AcOH (3 mL), the crude product was purified by MPLC using 4:1 EtOAc:hexanes, converted to the corresponding TFA salt and lyophilized. Yield of the title product as TFA salt: 182.3 mg (17%); <sup>1</sup>H NMR

(400 MHz, CD<sub>3</sub>OD)  $\delta$  1.60 (s, 9 H), 1.76-1.79 (m, 1 H), 1.89-2.04 (m, 2 H), 2.18-2.26 (m, 1 H), 3.64-3.69 (m, 1 H), 3.84-3.90 (m, 1 H), 4.28-4.34 (m, 1 H), 4.53-4.59 (m, 1 H), 4.66-4.71 (m, 1 H), 7.21 (dd,  $J=8.98, 1.95$  Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (d,  $J=1.95$  Hz, 1 H), 7.75-7.79 (m, 3 H); MS (ESI) (M+H)<sup>+</sup> = 414.0.

5

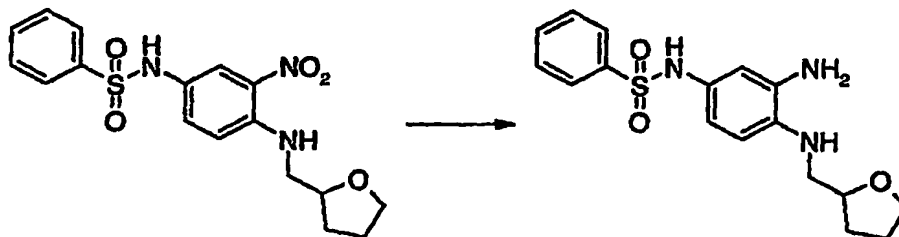
**Step B. *N*-[3-nitro-4-[[tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide**



Following the procedure for Step C in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), tetrahydrofurylamine (0.42 mL, 1.2 eq), EtOH (12 mL) and H<sub>2</sub>O (3 mL), the crude product was purified by MPLC using 1:1 heptane:EtOAc to afford the title compound as a bright red solid (749.7 mg, 59%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.62-1.73 (m, 1 H), 1.94-2.13 (m, 3 H), 3.27-3.47 (m, 2 H), 3.80-3.98 (m, 2 H), 4.15-4.22 (m, 1 H), 6.51 (s, 1 H), 6.81 (d,  $J=9.18$  Hz, 1 H), 7.35 (dd,  $J=8.98, 2.54$  Hz, 1 H), 7.44-7.48 (m, 2 H), 7.55-7.59 (m, 1 H), 7.63 (d,  $J=2.73$  Hz, 1 H), 7.69-7.72 (m, 2 H), 8.18-8.20 (m, 1 H).

15

**Step C. *N*-[3-amino-4-[[tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide**



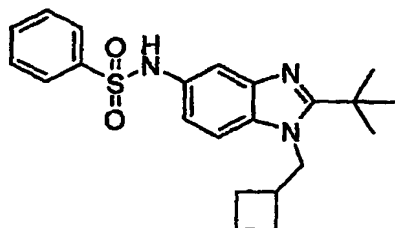
20

Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[[tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide (749.7 mg, 2 mmol) and a catalytic amount of 10% Pd/C in EtOAc (50 mL), LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step.

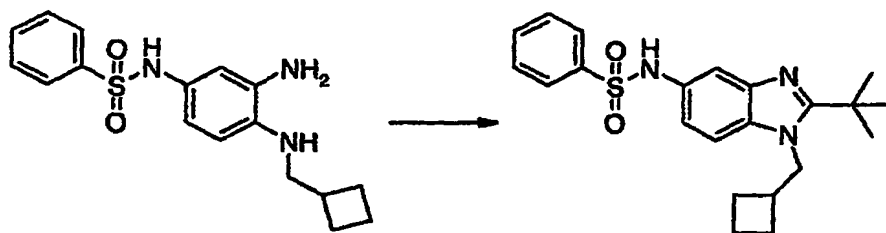
Yield: 597.2 mg, 86%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61-1.70 (m, 2 H), 1.89-1.96 (m, 2 H), 2.01-2.09 (m, 1 H), 2.97-3.02 (m, 1 H), 3.12-3.16 (m, 1 H), 3.34-3.59 (m, 3 H), 3.74-3.90 (m, 2 H), 6.28 (s, 1 H), 6.33 (dd,  $J=8.20, 2.34$  Hz, 1 H), 6.44 (d,  $J=8.40$  Hz, 1 H), 6.53 (d,  $J=2.34$  Hz, 1 H), 7.39-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.68-7.72 (m, 2 H).

### Example 19

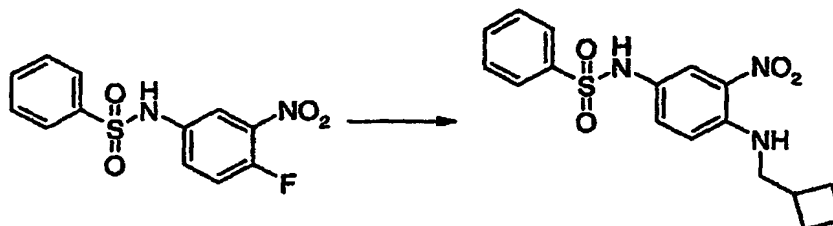
*N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



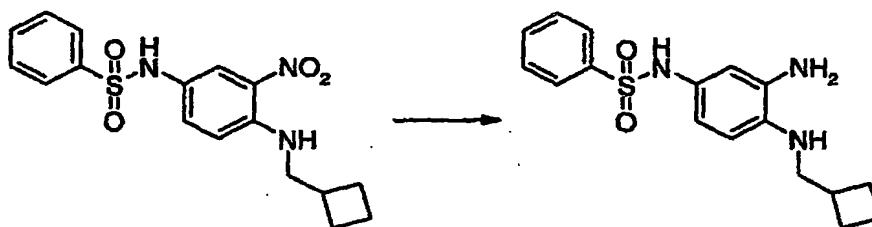
**Step A.** *N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



Following the procedure for Step A in Example 17, using *N*-[3-amino-4-((cyclobutylmethyl)amino)phenyl]-benzenesulfonamide (763.8 mg, 2.30 mmol) (for preparation, see the following steps B and C),  $\text{CH}_2\text{Cl}_2$  (40 mL), catalytic DMAP and pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (9 mL), the crude product was purified by MPLC using 1:1 hexanes:EtOAc, followed by reversed-phase HPLC using 20-65% MeCN in  $\text{H}_2\text{O}$ . The compound was lyophilized to afford the title compound as its TFA salt (226.8 mg, 19%);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.60 (s, 9 H), 1.81-1.93 (m, 2 H), 2.01-2.07 (m, 4 H), 2.78-2.83 (m, 1 H), 4.55 (d,  $J=6.44$  Hz, 2 H), 7.22 (dd,  $J=8.98, 1.95$  Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (dd,  $J=1.95, 0.59$  Hz, 1 H), 7.70 (dd,  $J=8.98, 0.59$  Hz, 1 H), 7.76-7.79 (m, 2 H); MS (ESI)  $(\text{M}+\text{H})^+ = 398.0$ .

**Step B. *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide**

Following the procedure for Step C in Example 17, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), cyclobutylmethylamine (345.7 mg, 1.2 eq),  
5 EtOH (12 mL) and H<sub>2</sub>O (5 mL) The crude product was purified by MPLC using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (857.7 mg, 70%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.73-1.78 (m, 2 H), 1.88-2.00 (m, 2 H), 2.13-2.21 (m, 2 H), 2.62-2.73 (m, 1 H), 3.27-3.30 (m, 2 H), 6.44 (s, 1 H), 6.78 (d, *J*=9.18 Hz, 1 H), 7.36 (dd, *J*=9.08, 2.44 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.55-7.60 (m, 1 H),  
10 7.66 (d, *J*=2.73 Hz, 1 H) 7.72-7.74 (m, 2 H), 7.93-7.98 (br s, 1 H).

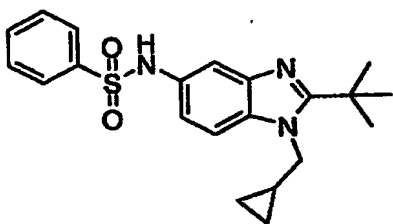
**Step C. *N*-[3-amino-4-[(cyclobutylmethyl)amino]phenyl]-benzenesulfonamide**

Following the procedure for Step E in Example 3, using *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (857.7 mg, 2.37 mmol) and a catalytic amount of 10% Pd/C in EtOAc (25 mL) and shaking for 48 h, LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 763.8 mg, 97%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.68-1.78 (m, 2 H), 1.86-1.98 (m, 2 H), 2.08-2.16 (m, 2 H), 2.54-2.62 (m, 1 H), 3.04 (d, *J*=7.42 Hz, 2 H), 3.11-3.42 (brs, 2 H), 6.28-3.31 (br. s., 1 H), 6.33 (dd, *J*=8.40, 2.34 Hz, 1 H), 6.43 (d, *J*=8.40 Hz, 1 H), 6.56 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).  
15  
20

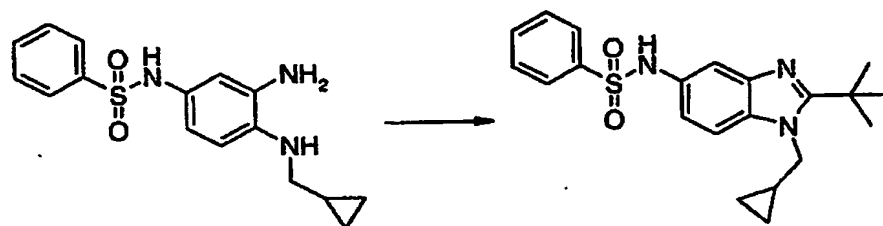
**Example 20**



***N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**

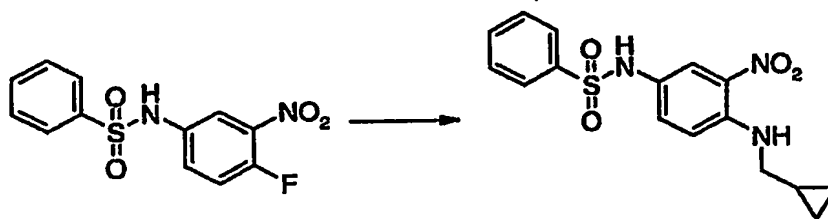


**Step A. *N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



Following the procedure for Step A in Example 17, using *N*-[3-amino-4-[(cyclopropylmethyl)amino]phenyl]-benzenesulfonamide (736.4 mg, 2.32 mmol) (for preparation, see the following steps B and C),  $\text{CH}_2\text{Cl}_2$  (50 mL), catalytic DMAP and pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (10 mL), the crude product was purified by reversed-phase HPLC using 15-45% MeCN in  $\text{H}_2\text{O}$ . The compound was lyophilized to afford the title compound as its TFA salt (50 mg, 4.2%);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.57-0.61 (m, 2 H), 0.65-0.70 (m, 2 H), 1.22-1.25 (m, 1 H), 1.62 (s, 9 H), 4.47 (d,  $J=6.44$  Hz, 2 H), 7.23 (dd,  $J=9.08$ , 2.05 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.55 (m, 1 H), 7.62 (d,  $J=1.95$  Hz, 1 H), 7.74 (d,  $J=8.98$  Hz, 1 H), 7.73-7.78 (m, 2 H); MS (ESI)  $(\text{M}+\text{H})^+ = 384.0$ .

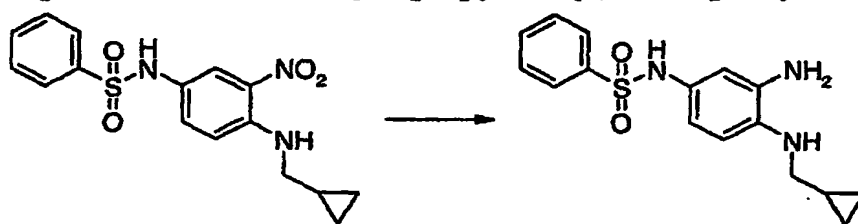
**Step B. *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide**



Following the procedure for Step C in Example 17, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol) and cyclopropylmethylamine (0.4 mL, 1.2

eq) in EtOH (12 mL) and H<sub>2</sub>O (5 mL). The crude product was purified by MPLC using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (828.3 mg, 71%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.29-0.33 (m, 2 H), 0.63-0.67 (m, 2 H), 1.14-1.19 (m, 1 H), 3.13 (dd, *J*=7.03, 4.88 Hz, 2 H), 6.42 (s, 1 H), 6.76 (d, *J*=9.37 Hz, 1 H), 7.36 (dd, *J*=9.18, 2.54 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.56-7.59 (m, 1 H), 7.67 (d, *J*=2.54 Hz, 1 H), 7.71-7.74 (m, 2 H), 8.07-8.13 (m, 1 H).

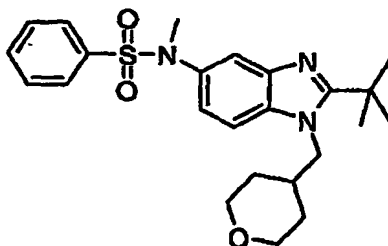
**Step C. *N*-[3-amino-4-[(cyclopropylmethyl)amino]phenyl]-benzenesulfonamide**



Following the procedure for Step E in Example 3, using *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (828.3 mg, 2.38 mmol), a catalytic amount of 10% Pd/C in EtOAc (30 mL). LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 736.4 mg, 100%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.20-0.24 (m, 2 H), 0.53-0.58 (m, 2 H), 1.08-1.12 (m, 1 H), 2.87 (d, *J*=7.03 Hz, 2 H), 3.28-3.48 (br. s., 2 H), 6.27-6.31 (br. s., 1 H), 6.31-6.34 (m, 1 H), 6.39-6.41 (m, 1 H), 6.57 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.49-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

**Example 21**

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**

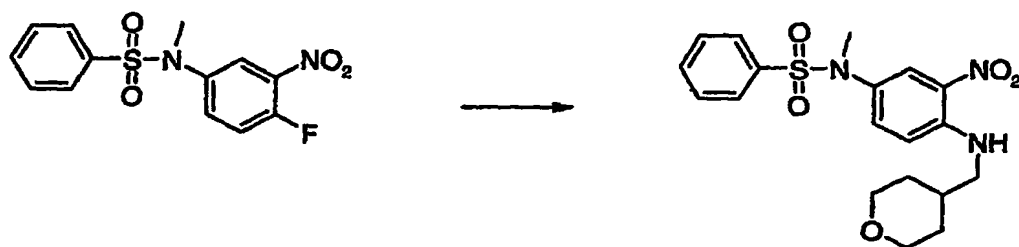


**Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



Following the procedure for Step E in Example 4, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (109 mg, 0.290 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride (0.039 mL, 0.319 mmol) and DMAP (7 mg, 0.058 mmol) in 3 mL of DCM. The second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 60 mg (37%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.55 (m, 2H), 1.60 (m, 2H), 1.68 (s, 9H), 2.37 (m, 1H), 3.27 (s, 3H), 3.36 (ddd, *J* = 11.57, 2.64 Hz, 2H), 3.93 (d, *J* = 3.52 Hz, 1H), 3.96 (m, 1H), 4.53 (d, *J* = 7.42 Hz, 2H), 7.31 (dd, *J* = 8.98, 1.95 Hz, 1H), 7.54 (m, 5H), 7.68 (m, 1H), 7.89 (d, *J* = 8.98 Hz, 1H); MS (ESI) (*M*+*H*)<sup>+</sup> 442.3.

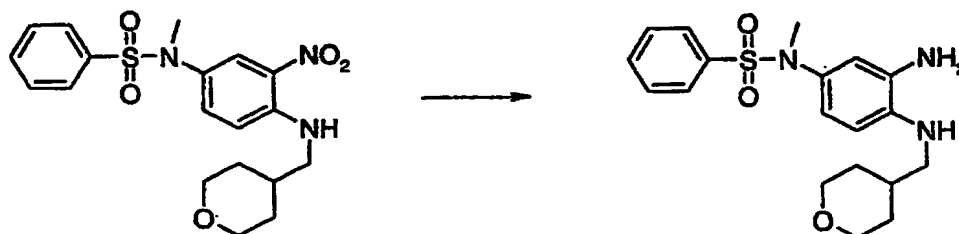
**Step B. *N*-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}benzenesulfonamide**



Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (100 mg, 0.322 mmol), 4-aminomethyltetrahydropyran (45 mg, 0.386 mmol) and TEA (0.070 mL, 0.483 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO<sub>4</sub> solution, saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was purified by silica gel flash chromatography using a linear gradient of 30-50% EtOAc / hexanes. Yield: 123 mg (94%); <sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ 1.44 (m,

2H), 1.74 (m, 1H), 1.77 (m, 1H), 1.96 (m, 1H), 3.13 (s, 3H), 3.23 (dd,  $J = 6.74$ , 5.57 Hz, 2H), 3.43 (ddd,  $J = 11.81$ , 2.15, 2H), 4.40 (dd,  $J = 11.13$ , 3.91 Hz, 2H), 6.84 (d,  $J = 9.18$  Hz, 1H), 7.49 (m, 3H), 7.61 (m, 3H), 8.21 (m, 1H).

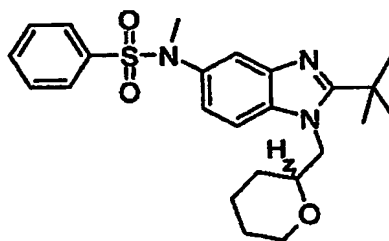
5 **Step C. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide**



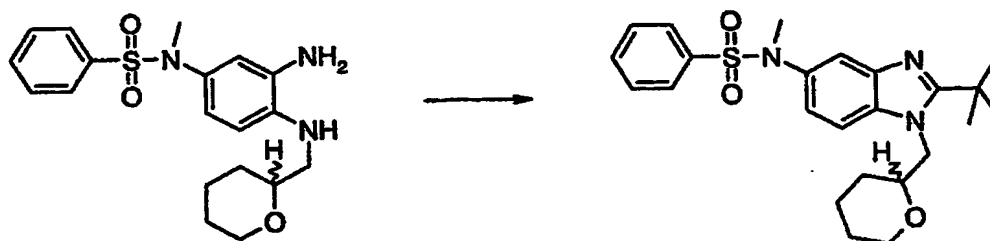
- 10 Following the procedure for Step E in Example 3, using *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}benzenesulfonamide (118 mg, 0.291 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 109 mg (99%); MS (ESI) ( $M+H$ )<sup>+</sup> 376.16.

15 **Example 22**

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



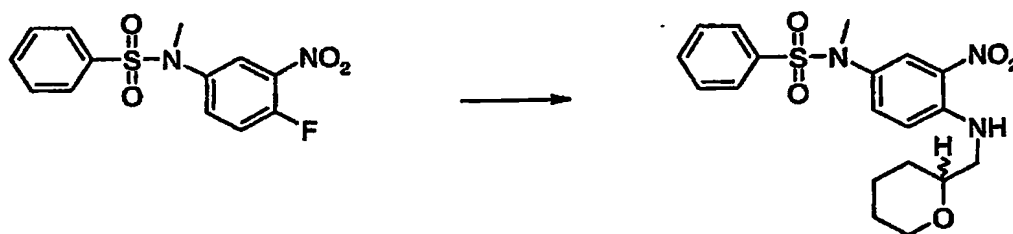
20 **Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



Following the procedure for Step E in Example 4, using *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide (47 mg, 0.125 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride (0.017 mL, 0.138 mmol) and DMAP (3 mg, 0.025 mmol) in 3 mL of DCM. The second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH<sub>3</sub>CN/H<sub>2</sub>O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 33 mg (48%); <sup>1</sup>H NMR (400 MHz, METHANOL-D<sub>4</sub>) δ 1.50 (m, 2H), 1.58 (m, 3H), 1.67 (s, 9H), 1.88 (m, 1H), 1.91 (m, 1H), 3.22 (ddd, J = 11.47, 2.64 Hz, 1H), 3.27 (s, 3H), 3.85 (m, 2H), 4.65 (m, 2H), 7.29 (dd, J = 9.08, 2.05 Hz, 1H), 7.51 (d, J = 1.56 Hz, 1H), 7.54 (m, 3H), 7.68 (m, 1H), 7.87 (d, J = 8.98 Hz, 1H); MS (ESI) (M+H)<sup>+</sup> = 442.3. Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S+1.5 TFA + 0.1 H<sub>2</sub>O: C, 52.78; H, 5.36; N, 6.84. Found: C, 52.83; H, 5.37; N, 6.90.

15

**Step B. *N*-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}benzenesulfonamide**

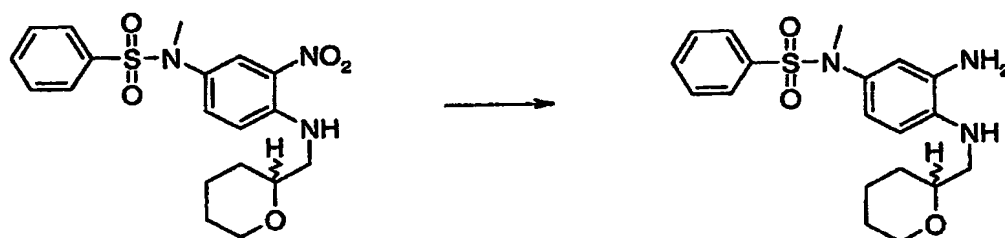


20

Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzene sulfonamide (50 mg, 0.161 mmol), 2-aminomethyltetrahydropyran hydrochloride (30 mg, 0.193 mmol) and TEA (0.056 mL, 0.403 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO<sub>4</sub> solution, saturated NaHCO<sub>3</sub> solution, brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was purified by silica gel flash chromatography using first DCM and then

EtOAc as eluent. Yield: 58 mg (89%);  $^1\text{H}$  NMR (400 MHz,  $\text{CHLOROFORM-D}$ )  $\delta$  1.46 (m, 1H), 1.55 (d,  $J = 7.03\text{Hz}$ , 2H), 1.60 (m, 2H), 1.67 (m, 1H), 1.91 (m, 1H), 3.13 (s, 3H), 3.29 (m, 1H), 3.37 (m, 1H), 3.50 (ddd,  $J = 11.33, 2.93\text{Hz}$ , 1H), 3.62 (m, 1H), 4.06 (m, 1H), 6.83 (d,  $J = 9.37\text{Hz}$ , 1H), 7.46 (dd,  $J = 9.37, 2.54\text{Hz}$ , 1H), 7.50 (m, 2H), 7.57 (m, 2H), 7.61 (m, 1H), 8.33 (m, 1H).

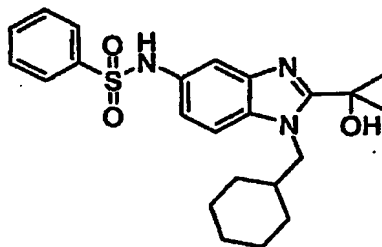
**Step C. *N*-[3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl]-*N*-methylbenzenesulfonamide**



Following the procedure for Step E in Example 3, using *N*-methyl-*N*-[3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl]benzenesulfonamide (55 mg, 0.136 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. Yield: 47 mg (92%); MS (ESI) ( $\text{M}+\text{H}$ ) $^+$  376.17.

**Example 23**

***N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



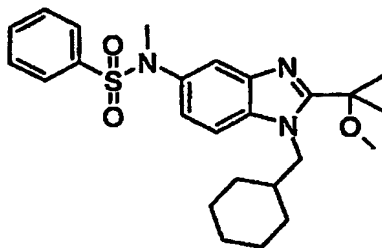
Diisopropylethylamine (291.4 mg, 2.25 mmol) was added into a solution of *N*-[3-amino-4-[(cyclohexylmethyl)amino]phenyl]benzene sulfonamide (540.1 mg, 1.50 mmol) (for preparation, see Steps B, C and D in Example 7) and 2-hydroxy isobutyric acid (171.8 mg, 1.65 mmol) in DMF (15 mL) at 0 °C. Stirring for 20 min., HATU (684.4 mg, 1.80 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50

mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (5 mL) in a sealed tube. The solutions were heated at 140°C using a Personal Chemistry Smith Synthesizer microwave instrument for 30 min.

- 5 Upon evaporation of the solvent, the residue was diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, the residue was purified by MPLC (EtOAc on silica gel) to give 364.6 mg (57%) of a white solid as the title compound. Part of the product was converted to TFA salt. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ1.17
- 10 (m, 5 H), 1.56 (m, 2 H), 1.70 (m, 3 H), 1.76 (s, 6 H), 2.09 (m, 1 H), 4.48 (d, J=7.62 Hz, 2 H), 7.23 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.72 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H); MS (ESI) (M+H)<sup>+</sup> = 428.0; Anal. Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>S+1.2TFA: C, 54.05; H, 5.39; N, 7.45. Found: C, 54.09; H, 5.50; N, 7.42.

15 **Example 24**

***N*-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide**



- Sodium hydride (31.2 mg, 0.78 mmol) was added into a solution of *N*-[1-
- 20 (cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (111.0 mg, 0.26 mmol) (for preparation, see Example 23) in THF (10 mL) at 0 °C. Stirring for 30 min., methyl iodide (145.9 mg, 1.03 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with saturated NaHCO<sub>3</sub> (2 mL), and extracted with EtOAc (2x50 mL). The combined
- 25 organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 110.3mg (93%) of colorless syrup as the title compound, which was converted to TFA salt as a white solid. <sup>1</sup>H NMR (400 MHz,

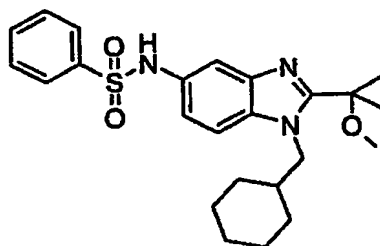
101195

CD<sub>3</sub>OD):  $\delta$  1.21 (m, 5 H), 1.62 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.79 (s, 6 H), 2.13 (m, 1 H), 3.27 (s, 3 H), 3.31 (s, 3 H), 4.46 (d,  $J=7.62$  Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 1 H), 7.55 (m, 4 H), 7.67 (m, 1 H), 7.76 (m, 1 H); MS (ESI) (M+H)<sup>+</sup> = 456.0; Anal. Calcd for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>S+0.8TFA+0.6H<sub>2</sub>O: C, 57.29; H, 6.33; N, 7.54.

5 Found: C, 57.34; H, 6.31; N, 7.33.

### Example 25

*N*-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



10

Following the same procedure in Example 24, using sodium hydride (25.0 mg, 0.63 mmol), *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (89.3 mg, 0.21 mmol) (for preparation, see Example 23) and methyl iodide (27.4 mg, 0.19 mmol) in THF (10 mL). The desired title compound was purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 34.8 mg (38%) of colorless

15

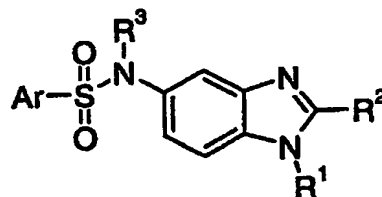
syrup, which was converted to TFA salt as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  1.18 (m, 5 H), 1.59 (m, 2 H), 1.68 (m, 1 H), 1.74 (m, 2 H), 1.78 (s, 6 H), 2.09 (m, 1 H), 3.30 (s, 3 H), 4.42 (d,  $J=7.42$  Hz, 2 H), 7.23 (dd,  $J=9.08, 2.05$  Hz, 1 H), 7.47 (m, 2 H), 7.55 (m, 1 H), 7.58 (d,  $J=2.15$  Hz, 1 H), 7.72 (d,  $J=9.18$  Hz, 1 H), 7.80 (m, 2 H); MS (ESI) (M+H)<sup>+</sup> = 442.0; Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S+0.9TFA+0.5H<sub>2</sub>O: C, 56.01; H, 5.99; N, 7.60. Found: C, 55.97; H, 6.00; N, 7.47.

20



What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:



I

wherein

$R^1$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl,  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{4-8}$ cycloalkenyl, and  $C_{3-6}$ heterocycloalkyl used in defining  $R^1$  is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

$R^2$  is selected from  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl, wherein said  $C_{1-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-8}$ cycloalkenyl- $C_{1-4}$ alkyl used in defining  $R^2$  is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

$R^3$  is selected from -H,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl, and  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl; and

Ar is selected from  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl, wherein said  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl are optionally substituted with one or more groups selected from  $C_{1-3}$ alkyl, methoxy and halogen.

2. A compound as claimed in claim 1, wherein

$R^1$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-6}$ cycloalkenyl- $C_{1-4}$ alkyl and  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl, wherein said  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl,  $C_{4-6}$ cycloalkenyl- $C_{1-4}$ alkyl and  $C_{3-6}$ heterocycloalkyl- $C_{1-4}$ alkyl used in defining  $R^1$  is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, hydroxy and amino;

$R^2$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-6}$ cycloalkenyl- $C_{1-4}$ alkyl, wherein said  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl, and  $C_{4-6}$ cycloalkenyl- $C_{1-4}$ alkyl used in defining  $R^2$  is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy and hydroxy;

$R^3$  is selected from -H and  $C_{1-3}$ alkyl; and

Ar is selected from phenyl and  $C_{3-6}$ heteroaryl, wherein said phenyl and  $C_{3-6}$ heteroaryl are optionally substituted with one or more groups selected from methyl, methoxy, fluoro, chloro, bromo and iodo.

10

3. A compound as claimed claim 1,

$R^1$  is selected from cyclopentyl-methyl, cyclohexyl-methyl, cyclobutyl-methyl, tetrahydropyranyl-methyl, tetrahydrofuranyl-methyl, morpholinyl-methyl, piperdinylethyl, N-methyl-piperdinyl-methyl and piperdinyl-methyl;

15  $R^2$  is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-hydroxy-propyl, 2-methoxy-2-propyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-buten-1-yl, ethyl, and 2-propyl;

$R^3$  is selected from -H and methyl; and

Ar is selected from phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl, wherein said phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl are optionally substituted with one or more groups selected from methyl, methoxy, fluoro and chloro.

4. A compound as claimed in claim 1, wherein

25  $R^1$  is cyclohexyl-methyl;

$R^2$  is t-butyl;

$R^3$  is selected from -H and methyl; and

Ar is selected from phenyl, pyridyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl, wherein said phenyl, pyridyl, thiazolyl, thienyl, isoxazolyl, imidazolyl, and pyrazolyl are optionally substituted with one or more methyl groups.

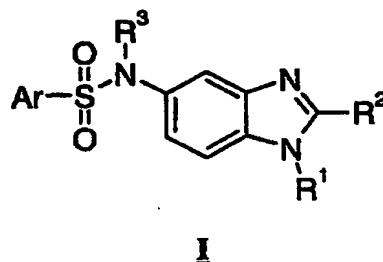
30

5. A compound selected from:

- N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide;
- N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide;
- 5 *N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide;
- N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide;
- N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-4-sulfonamide;
- 10 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,3,5-tetramethyl-1*H*-pyrazole-4-sulfonamide;
- N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide;
- 15 *N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzene sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;
- 20 *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethyl-3-butenyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;
- 25 *N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide;
- 30 *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide;

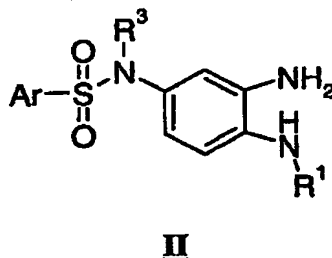
- N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide;  
*N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;  
5 *N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;  
*N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;  
*N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;  
10 *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;  
*N*-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide;  
15 *N*-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]—benzenesulfonamide; and pharmaceutically acceptable salts thereof.
6. A compound according to any one of claims 1-5 for use as a medicament.
- 20 7. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the therapy of pain.
8. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of anxiety disorders.
- 25 9. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.
- 30 10. A pharmaceutical composition comprising a compound according to any one of claims 1-5 and a pharmaceutically acceptable carrier.

5    12    A method of preparing a compound of formula I,



**comprising:**

reacting a compound of formula II,



with a compound of  $R^2COX$ , in the presence of a base, such as an alkylamine, and optionally a coupling reagent, such as HATU, EDC;  
wherein

**15**            **X is selected from Cl, Br, F and OH;**

**R<sup>1</sup>** is selected from C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl-C<sub>1-4</sub>alkyl, C<sub>4-8</sub>cycloalkenyl-C<sub>1-4</sub>alkyl, C<sub>3-6</sub>heterocycloalkyl-C<sub>1-4</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>4-8</sub>cycloalkenyl, and C<sub>3-6</sub>heterocycloalkyl, wherein said C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl-C<sub>1-4</sub>alkyl, C<sub>4-8</sub>cycloalkenyl-C<sub>1-4</sub>alkyl, C<sub>3-6</sub>heterocycloalkyl-C<sub>1-4</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>4-8</sub>cycloalkenyl, and C<sub>3-6</sub>heterocycloalkyl used in defining R<sup>1</sup> is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

R<sup>2</sup> is selected from C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkyl-C<sub>1-4</sub>alkyl, and C<sub>4-8</sub>cycloalkenyl-C<sub>1-4</sub>alkyl, wherein said C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkyl-C<sub>1-4</sub>alkyl, and C<sub>4-8</sub>cycloalkenyl-C<sub>1-4</sub>alkyl used in

defining  $R^2$  is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

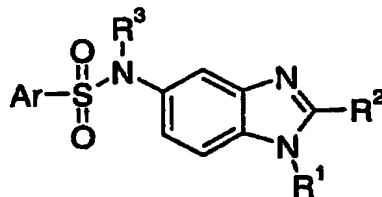
$R^3$  is selected from  $-H$ ,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl, and  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl; and

- 5       Ar is selected from  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl, wherein said  $C_{6-10}$ aryl and  $C_{3-6}$ heteroaryl are optionally substituted with one or more groups selected from  $C_{1-3}$ alkyl, methoxy and halogen.

03-01-05

**ABSTRACT**

Compounds of formula I or pharmaceutically acceptable salts thereof:



5

**I**

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Ar are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

256000